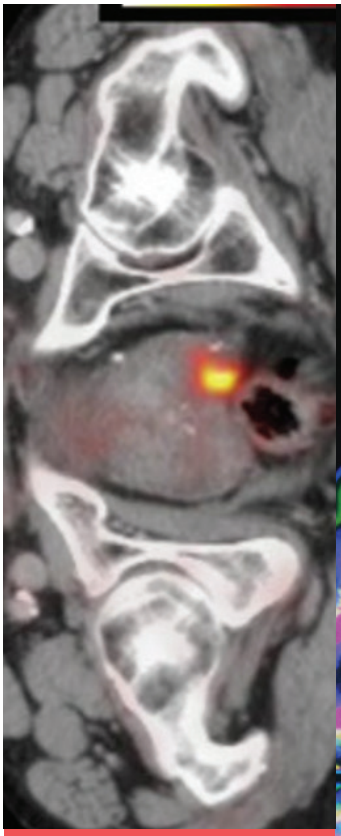
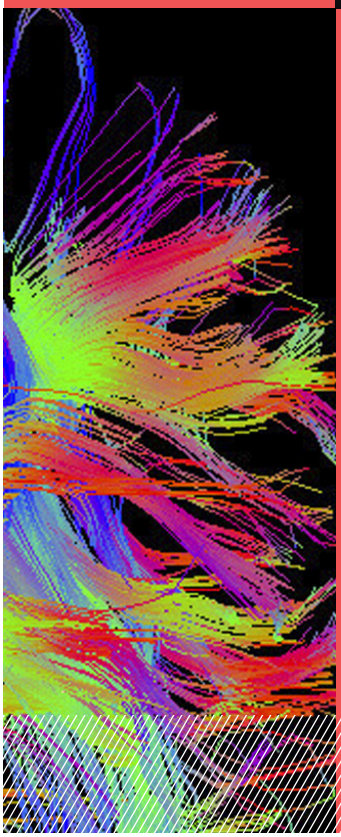


TRAIL

Translational Research and Advanced Imaging Laboratory

2011-2016 Activity Report

for Scientific Advisory Board



CLUSTER université de Bordeaux OF EXCELLENCE

INVESTISSEMENTS D'AVENIR

université de BORDEAUX

cnrs

Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

Table of contents

PREPARING THE FUTURE

ANNEX

Activity Report

This report refers to the 2011-2016 activity report sent to the French National Research Agency[1] in charge of the monitoring of LabEx programs.

[1] www.agence-nationale-recherche.fr/en/about-anr/investments-for-the-future/

Preparing the future

Cluster of Excellence of the University of Bordeaux

Higher education and research are key levers in achieving a new form of growth that is smarter, more sustainable and more inclusive, with the goal being to prepare for a knowledge society in which future generations can achieve fulfilment.
The University of Bordeaux and its partners intend to address this challenge by shaping a campus of excellence with an international reputation, uniting its research forces around high-level scientific pillars.
These are neuroscience, medical imaging, cardiology, public health, materials of the future, environment, archaeology, laser optics and digital technologies.
These priorities reflect the research strengths of the Bordeaux site whose excellence is clearly recognised in terms of the standards applicable to the discipline and its high international profile.

Certifications by the French national "Investments for the Future" scheme in 2011 have strengthened this dynamic of ambitious multidisciplinary projects. Today, these centers of excellence backed by innovative training off er great prospects for development, French research and the socioeconomic world.
The pursuit of excellence is thus at the heart of the development policy of the University of Bordeaux. Through this tremendous momentum, the University of Bordeaux is seeking to answer the challenges of our environment to prepare for tomorrow's society.

TRAIL : Translational Research and Advanced Imaging Laboratory

Medical imaging plays a central role in meeting public health challenges.

From a medical point of view, imaging provides an earlier, faster and more accurate diagnosis, as well as optimal therapeutic management adapted to the biology and genome of the patient. It also allows a more targeted drug delivery, better monitoring of the effectiveness of treatment and less invasive surgery because of the guidance it provides.

From an economic point of view, imaging optimizes care costs thanks to early diagnosis, optimal treatment and a shorter recovery time. It is also a source of industrial competitiveness.

The Translational Research and Advanced Imaging Laboratory (TRAIL) was accredited in July 2011 to exploit the multidisciplinarity and the translational forces of the Bordeaux imaging community. Teams aim at developing a research portfolio that adresses major health themes :

- Neurology
- Oncology
- Cardiology
- Pneumology
- Nephrology

Based on specific international competitive research domains in Bordeaux, 7 scientific pillars constitute the research :

- Interventional imaging and MRI guided HIFU : to further develop MRI HIFU towards treatment of tumors in particular for the liver and the kidney, as well as breast and prostate from large animals to clinical trials;
- New imaging sequences : to increase spatial and temporal resolutions, sensitivity, specificity to become more quantitative and to adapt NMR/MRI to biological systems;
- Dynamic nuclear polarization : to develop new Targeted DNP-Contrast Enhanced MRI for diagnosis through protease spotting;
- Tracers and contrast agents : to create responsive agents for molecular imaging, using different imaging modalities towards functional imaging (MR, PET and Optical);
- Biological bio-imaging marker s : to detect imaging biomarkers used for prediction and diagnosis of patients at risk, for evaluation of disease progression and evaluation of therapeutic interventions;
- Mathematical simulation and modeling : to compute patient-specific digital models from multimodal imaging data in order to reproduce diseases and treatments in silico;

› Cohort imaging methodology : to implement structural/ functional MRI (3T/7T) neuroimaging platform fields dedicated to translational research in the field of age-related disorders and neurodegenerative diseases.

Research teams focus on 4 main missions :

› To federate the entire scientifi c community through multidisciplinary projects in the field of medical imaging translational research and raise the international profile of Bordeaux research;

› To develop an area for collaborations with industrialists, laboratories and international partner;

› To accelerate the process of technology transfer

› To provide students with a range of internationally recognized training courses in medical imaging.

« TRAIL strongly impacts the Bordeaux imaging community by structuring 7 scientific pillars and by organizing the multidisciplinarity between 10 teams from 7 core laboratories. »

Professor Vincent Dousset, TRAIL director

2011-2016 Key figures

Governance

7 units

10 teams

260 persons in community

> A Board of trustees, a Steering Committee, Work-package Coordinators, a Scientific Advisory Board, an Evaluation Committee

> Director : Pr Vincent Dousset

Research

34 research projects

5.4M€ total research budget

4 registering at the french Software Protection Agency

10 Patent

1 startup

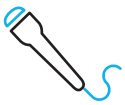
89 publications quoting TRAIL

94 scientific communication in international congress

Preparing the future

Scientific animation and training

37
International conferences in Bordeaux



15
association with international scientific events

62
students in the Master of BioImaging

4
TRAIL « scientific days »

Attractiveness

33
international academic collaborations

46
recrutments

8
visiting scholars

11.1M€
of cofunding

7
european projects

1
ERC starting

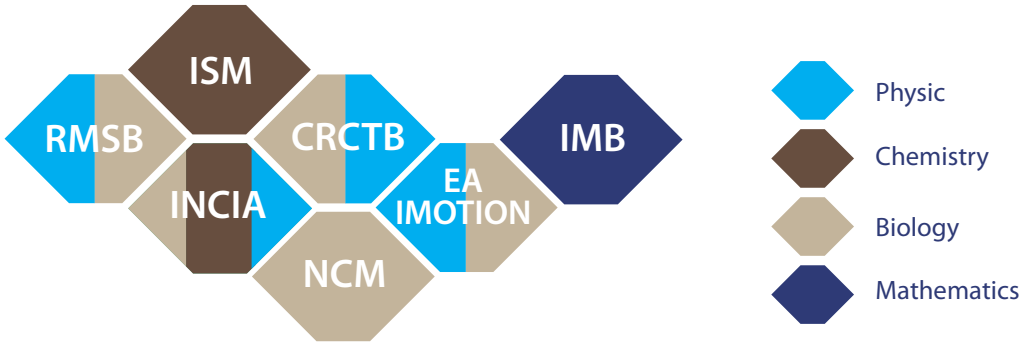
33
collaborations with industries

6
mobilities

Governance

1.1 CorePartners

TRAIL is a consortium of 7 multidisciplinary units (10 teams) on the same site: imaging clinicians, physicists, biologists, chemists, mathematicians and informaticians are all assets for developing competitive research.



RMSB: Magnetic Resonance of Biological Systems Laboratory
ISM: Molecular Sciences Institute (bio-active molecules and synthesis team and innovation in chemical synthesis team)
CRCTB: Cardio-Thoracic Research Center of Bordeaux (cardiac electrophysiology team and bronchial remodeling team)
INCIA: Aquitaine Institute for Cognitive and Integrative Neuroscience (neuroimaging and human cognition team and brain molecular imaging team)
NCM: Neurocentre Magendie (neuro-glia interactions team)
EA IMOTION: molecular imaging and innovative therapeutics in oncology team
IMB: Mathematical institute of Bordeaux (mathematical simulation and modelisation team)

The Community is composed of 260 persons : researchers, clinicians, Post-docs, PhD students, engineers working on complementary themes (see annex A.2 for details).

1.2 Governance boards

The governance of the LabEx TRAIL is formalized by a Consortium Agreement signed by all five institutional trustees (University of Bordeaux, CEA, CNRS, INSERM, INP).

Board of Trustees

- 5 members: University of Bordeaux, CEA, CNRS, INSERM, INP;
- Role: the Board of Trustees oversees the development of the LabEx, checks the adequacy between objectives and strategy.

Steering Committee

- 16 members: 10 representatives of laboratories, 5 representatives of thematic axes and the Director, who chairs the committee (see annex A.3 for details);
- Role: members of the Steering Committee meet monthly to define the development strategy, collaborative actions, guidelines of calls for proposals, and to discuss the budget.

Work-Packages Coordinators

- 7 Coordinators (one per work-package);
- Role : Coordinators define scientific themes for calls guidelines, are part of the research project selection process, and are involved in scientific animation.

Scientific Advisory Board

- 4 Members : international medical imaging researchers;
- Role : members evaluate TRAIL achievements and help the Steering Committee in defining strategy and development actions.

Governance

Director/ANR coordinator

- TRAIL Director is Pr Vincent Dousset; he is the "Coordinator" of the TRAIL program for the ANR;
- Role: the Director is in charge of the development of the LabEx, the coordination of 7 CorePartners, and the collaboration with all partners; he liaises with the Board of Trustees and IdEx Bordeaux and does a reporting to the ANR, to IdEx Bordeaux and to the Board of Trustees when necessary.

Evaluation Committee

- 2 Members: 2 regional scientists independent from TRAIL;
- Role: the Evaluation Committee evaluates scientific projects that were submitted to TRAIL calls and recommends projects to be granted on the basis of external scientific reviews.

Administrative Staff

- The administrative team is composed by the General Manager and the Scientific Animation Coordinator;
- Role: the administrative team set up procedures, implements actions, promotes the LabEx, and manages the budget in strong collaboration with the financial teams of the University of Bordeaux.

1.3 Monitoring and financial plan

Monitoring

- Developments are monitored by the Steering Committee and by the Director, in link with work-packages Coordinators, with the IdEx Bordeaux and with the Trustees. The Steering committee Members met 49 times over the 2011-2016 period. They are helped by i) Scientific Advisory Board Members for global scientific strategy (one meeting in 2015) and by ii) Work-packages Coordinators for TRAIL calls and for scientific animation;
- The Director of TRAIL reports to the National Research Agency (one report per year), to the Board of Trustees (two meetings : 2012, 2016) and to the IdEx of Bordeaux. Main governance actions are presented to the TRAIL Community during Annual General Assemblies.

Financial plan

The financial plan was defined as follows for the 2011-2016 period:

TRAIL OBJECTIVES	STRATEGY	PROGRAM	2011	2012	2013	2014	2015	2016	2011-2016
WORKING ON MAJOR PUBLIC HEALTH ISSUES	Showing importance of TRAIL research to society and scientific community								
DEVELOPING COMPETITIVE RESEARCH	Boosting existing research projects	Doctoral fellowship program	195K€				300K€	400K€	895K€
		Post-doctoral fellowship program			200K€	200K€	100K€	200K€	700K€
		Research projects consolidation program				220K€	180K€	111K€	510K€
	Supporting new research projects	Federative and emerging research program	299K€	1 151K€	694K€	70K€	400K€	688K€	3 303K€
	Strategical collective action	MRI time purchase program		57K€			421K€		477K€
FEDERATING THE COMMUNITY AND REINFORCING ATTRACTIVENESS	Governance, scientific animation, attractiveness	Governance (administration and communication actions, meetings, calls reviews, publication costs cofunding), scientific animation and training (summerschools, scientific event support, lectures, scientific day), mobilities	41K€	94K€	107K€	122K€	172K€	255K€	790K€
			535K€	1 302K€	1 001K€	612K€	1 572K€	1 654K€	6 675K€

The financial team of the IdEx Bordeaux is in charge of the management of TRAIL expenses, in deep integration with the TRAIL administrative team.

1.4 Support from the IdEx Bordeaux

LabEx are scientific pillars of IdEx and the objective of IdEx is to dedicate 80% of its funding to LabEx perimeter. IdEx accelerates the development of LabEx by helping them for the monitoring of programs, for the reinforcement of attractiveness, and for the deployment of cross-disciplinarity research projects.

Monitoring of the program:

i) The Director of TRAIL regularly presents main achievements of the LabEx to IdEx Bordeaux; LabEx project managers meet to discuss about procedures and best practices;
ii) The management of expenses was centralized by IdEx Bordeaux in 2014;
iii) The IdEx communication team produces communication documents for TRAIL (activity reports, booklets, flyers, TRAIL web site graphical charter);
iv) IdEx Bordeaux launched a study of TRAIL patents and publications (Via Inno program) to benchmark TRAIL scientific production with international teams.

Reinforcing attractiveness:

i) The 2 summerschools supported by TRAIL were also supported by IdEx (2014 Connectomics summerschool, 2015 Neurepiomics summerschool);
ii) TRAIL was granted by IdEx to welcome 8 international professors;
iii) TRAIL was granted by IdEx program with fundings for outgoing mobilities to Sherbrooke University and to Aarhus University;
iv) A doctoral fellow was granted by IdEx in collaboration with the Melbourne University (2013-2015, M. Lariviere).

IdEx Bordeaux supports cross-disciplinary research through "Inter-LabEx Program": i) TRAIL and CPU (Numerical certification and reliability) were granted in 2013 with 134 000 € for a neuroimaging data analysis project; ii) TRAIL and BRAIN (Bordeaux Region Aquitaine Initiative for Neurosciences) were granted by IdEx Bordeaux in 2014 with 146 000 € for the development of a new MRI method to assess hippocampal layer (Memo-ms project). CPU co-financed postdoctoral fellow and engineer positions (150 000 €) for a TRAIL project and BRAIN co-financed the Memos-ms project (120 000 €).

Also, IdEx Bordeaux and TRAIL have both supported the purchase of 3T MRI time dedicated to the TRAIL research projects developments.

Finally, TRAIL built links with other PIA programs (I-Share cohort, OFSEP cohort) and with the IHU LYRIC.

1.5 Mid-period audit by the ANR

TRAIL was audited by the international jury of the National Research Agency in June 2015: « (...) Overall the panel was very impressed by the scientific progress reported by the consortium: it has successful built an impressive collaborative network, potentially positioned to deliver in the future (...) ». (see annex A.4 for full evaluation)

Research achievements

2.1 Internal call procedure

To achieve main objective of translational and multidisciplinary research, TRAIL strategy was to set up a portfolio of research projects. They were selected through procedures for calls for proposals with international peer-review:

- Emerging calls support new projects looking to fund a proof of concept; the aim is to encourage the emergence of scientific breakthroughs. The selected projects are risky but have a high potential return on investment (18 months of funding, 35,000€-50,000€ maximum);
- Federative calls concern advanced projects that are seeking to accelerate cross-sectional research. These projects are coordinated by teams from several laboratories on transdisciplinary topics (36 months of funding, 200,000€ maximum);
- Doctoral Fellowship calls and Postdoc calls allow the recruitment of a Doc/Postdoc to extend the development of an already awarded project (24 to 36 months of funding, 100,000€ maximum);
- Open calls concern already granted projects that propose to broaden and consolidate their research themes (50,000€-60,000€ maximum).

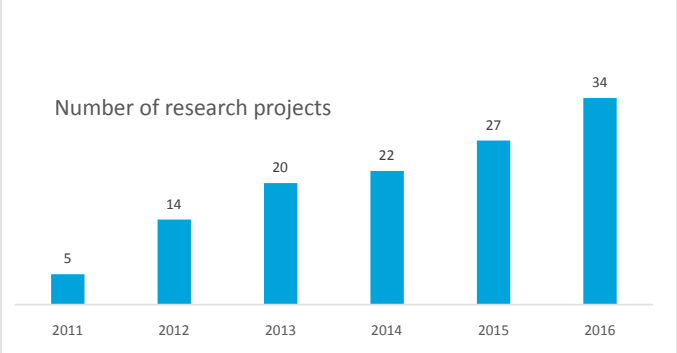
The funding from TRAIL aims at financing human resources costs and running costs. Financial support for equipment is limited to 15,000€ per project.
Each submission to a call is analyzed by 2 international scientific reviewers who assess the scientific originality of the project, the quality of the team and of the development plan. Their reviews are given to the Evaluation Committee which recommends projects to be granted, under supervision of the Director of TRAIL.

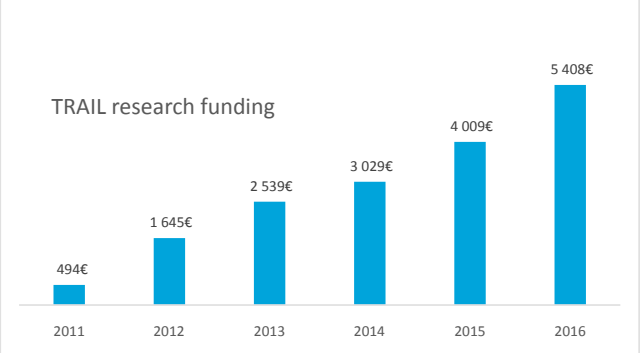
For the monitoring, project leaders report the achievements of research as follows:

- An annual written report describing the scientific developments, recruitments, academic and industrial collaborations, publications, distinctions and awards, dissemination of knowledge, co-funding, expenses;
- An oral scientific presentation during the annual General Assembly to present the project;
- An oral scientific presentation during the annual TRAIL Scientific Day to present research achievements.

From 2011 to 2016, 34 research projects were funded, for a total budget of 5,4M€:

- In 2011: 5 federative projects, for a total budget of 494K€;
- In 2012: 4 federative projects and 5 emerging projects for a total budget of 1151K€;
- In 2013: 4 federative projects, 2 emerging projects and 2 PhD funding for a total budget of 894K€;
- In 2014: 2 emerging projects, 4 consolidated projects and 3 PhD funding for a total budget of 490K€;
- In 2015: 2 federative projects, 3 emerging projects, 3 consolidated projects, 3 PhD funding and 1 Post-Doc funding, for a total budget of 980K€;
- In 2016: 3 federative projects, 4 emerging projects, 2 consolidated projects, 4 PhD funding and 2 Post-Doc funding, for a total budget of 1399K€.





	Interventional imaging and MRI guided HIFU	New imaging sequences	DNP	Tracers & contrast agents	Biological Bio-imaging markers	Mathema-tic simu-lation and modeling	Cohort imaging methodology		
Neuro		179 600 €		48 800 €	1 256 233 €		572 330 €	2 056 963 €	38,0%
Onco	30 000 €		482 500 €	784 000 €	35 000 €	530 000 €		1 861 500 €	34,4%
Cardio	400 000 €	250 000 €		185 000 €	295 000 €			1 130 000 €	20,9%
Pneumo					40 000 €	35 000 €	234 448 €	309 448 €	5,7%
Nephro						50 000 €		50 000 €	0,9%
	430 000 €	429 600 €	482 500 €	1 017 800 €	1 626 233 €	615 000 €	806 778 €	5 407 911 €	100%
	8%	8%	9%	19%	30%	11%	15%	100%	

2.2 Research portfolio

The input of the 34 TRAIL granted projects made the cement to build translational research, and gave the capability to achieve research from the most basic to clinical application and cohort imaging in link with hospitals.

MOD
Mathematical modeling of the response to antiangiogenic drugs via medical imaging,
2013, 380 000 € (onco)

ARM
Automatic assessment of Radiofrequency ablation Margins,
2016, 150 000 € (onco)

NEKOMRI
MRI sequence for bronchial wall segmentation and analysis,
2014, 35 000 € (pneumo)

HETEROMRMAP
MR mapping of renal function heterogeneity to characterize parenchymal nephropathies,
2016, 50 000 € (nephro)

BIOPSYPROSTAPROBE
Antibody-based fluorescence probe for biopsy guidance of prostate cancer,
2014, 35 000 € (onco)

GMCOG
Grey matters! Toward a better understanding of grey matter alteration and cognitive deficit associated with multiple sclerosis,
2016, 200 000 € (neuro)

IPALICA
Inflammatory pathways leading to intracranial aneurysm growth,
2015, 35 000 € (neuro)

STEAMRI
Whole lung oxygen-enhanced imaging in humains using MRI,
2016, 40 000 € (pneumo)

ABACI
Automated Brain anatomy softwares for cohort imaging,
2012, 314 830 € (neuro)

ACTE
Cognitive training and brain functional connectivity,
2012, 130 000 € (neuro)

TRAIL&TRACKS
Atlasing white matter tracts,
2011, 97 500 € (neuro)

ADPP
Brain Topology of AD presymptomatic phase,
2015, 30 000 € (neuro)

COBRASCAN
Quantitative computed tomography for phenotyping COPD within COBRA cohort,
2013, 234 448 € (pneumo)

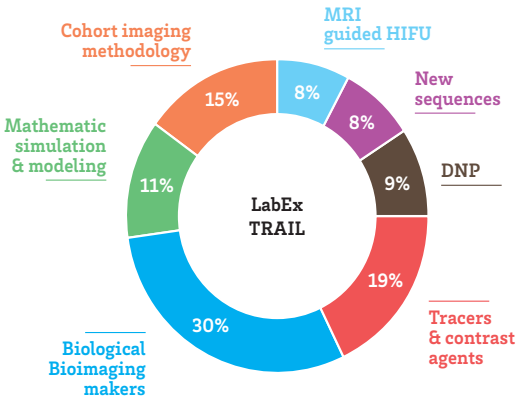
HIFU
Alteration of the blood brain barrier induced by HIFU,
2012, 30 000 € (onco)

MRGHIFU
Methodological developments for applications of HIFU in cardiology and oncology,
2013, 400 000 € (cardio-onco)

HR-DTI
Developping High-Resolution DTI method,
2012, 130 000 € (neuro)

MDMRI
Methodological Developments in High Spatial/Angular-resolution DTI for ex-vivo validation of tractography,
2016, 49 600 € (neuro)

NEWFISP
Improving MRI resolution to correctly MRI-diagnose cardiac pathologies and metastases,
2012, 250 000 € (cardio-onco)



TRAILDNP
To improve in vivo DNP in mice at 0.2T,
2011, 242 500 € (neuro)

ONCOFLUX
Metabolic flux MR imaging in tumors,
2013, 240 000 € (onco)

FITTING
18F-Bioorthogonal probe for imaging traumatic brain injury glycol-biomarkers,
2016, 48 800 € (neuro)

TARGLIN
Imaging siRNA targeting of glioblastoma using peptide-based nanoparticules,
2015, 150 000 € (onco)

NEPMIP
NanoEmulsion Platform for Magnetic Particle Imaging,
2015, 35 000 € (cardio)

NANOMULTIMAG
Smart multimodal nanoprobes for MRI/MPI/NIRF imaging with magneto/optical contrast agents for atheroma plaque targeting,
2016, 150 000 € (cardio)

TBI
Longterm neurovascular unit changes after mild traumatic brain injury: potential biomarker & Vasc-TBI,
2015, 150 000 € (neuro)

IBIO-NI
New Imaging Biomarkers of neuroinflammation such as MS,
2012, 310 654 € (neuro)

INNES
Lactate and neuronal metabolism,
2011, 300 579 € (neuro)

TRANSFEAR
Cerebral structure changes involved in pathological fear recovery,
2012, 130 000 € (neuro)

MIMATHUMAB
Molecular Imaging of Atheroma with Human Antibody,
2012, 295 000 € (cardio)

SCICOG&REACTIV
Imaging biomarker in MS,
2011, 130 000 € (neuro)

IMMELAPT
Detecting tumors using SPECT molecular imaging and optimized aptamers,
2012, 250 000 € (onco)

PRITOR
NeuroPeptide Receptors Imaging for TumOR Targeting,
2013, 90 000 € (onco)

SUPSIFLU
Supported Silyl Fluorination,
2013, 130 000 € (onco)

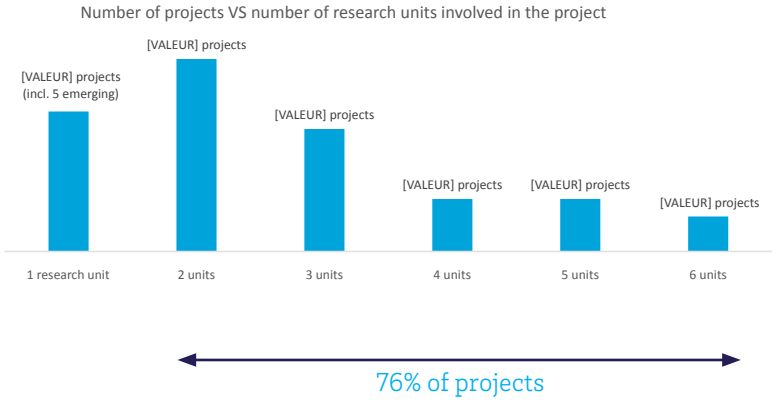
PIAF
18F for PET-imaging angiogenesis,
2011, 164 000 € (onco)

(see annex B.1 for projects abstracts, and see annex B.2 for achievements)

Research achievements

2.3 Interdisciplinarity

Research in TRAIL is based on multidisciplinary teams : 76% of TRAIL funded projects rely, at least, on expertises of 2 different research units:



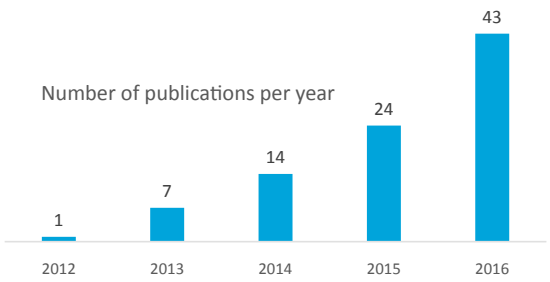
2.4 Imaging Platform

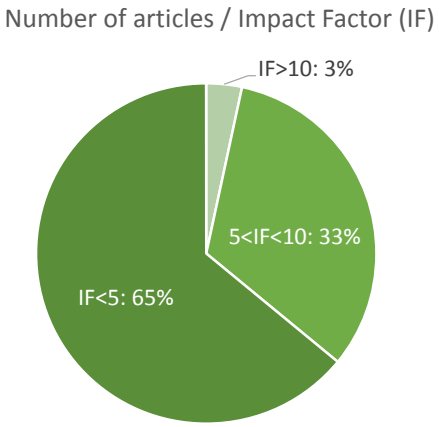
Researchers have access to two state-of-the-art imaging platforms in Bordeaux: i) UMS-CNRS-3767: Biomedical science imaging platform, University of Bordeaux, in association with the University Hospital Pellegrin; ii) PTIB: Biomedical Innovation Technological Platform, University of Bordeaux, in association with the South University Hospital. Research teams can also benefit from top-notch equipment from IHU LYRIC cardiology imaging platform.

2.5 Scientific communication

Publications in peer-reviewed journals

› TRAIL researchers have published 89 publications quoting TRAIL over the 2011-2016 period (see annex B.31 for details): Nature Neurosciences, Angewandte Chemie, Biological Psychiatry, Theranostics, Nature Reviews Nephrology, Thorax, JNNP journal, Stroke, Chem Communication, NeuroImage, Org Letters, NeuroImage, Radiology, J Nucl Med, Human Molecular genetics, Human Brain Mapping, Brain Behavior and Immunity, Chemistry a European Journal, Nature Scientific Reports,...





› 12 TRAIL publications belong to the 10% of most quoted publications in the world over the 2011-2015 period (26% of publications of that period)

› The average Field-Weighted Citation Impact is 1,46[1]

› Publications costs of TRAIL quoted publications are co-funded by the LabEx

Scientific communication

Researchers from the Community have given 94 scientific communications in international events (see annex B.32 for details): ISMRM, ECTRIMS, IMSCOGS, Human Brain Mapping, ESMRMB, Interventional MRI Symposium, Congress of the European Association of Nuclear Medicine, FENS, European Congress of Radiology,...

[1] This metric indicates how the number of citations received by a publications compares with the average number of citations received by all other similar publications ; a Field-Weighted Citation Impact of greater than 1.00 indicates that the publications have been cited more than would be expected based on the world average for similar publications (46% more)

2.6 Patents

By the end of 2016, 10 patents issued from TRAIL have been registered (see annex B.4 for details):

5
patents on
cardiology topics

1
patents on
neurology topics

3
patents on
oncology topics

1
patents on
pneumology topics

Regarding patents, Aquitaine Science Transfer (AST) - the technology transfer agency - represents the trustees for intellectual property negotiations with industrialists.

2.7 Startup

In 2016, the startup « Nenuphar » was created, based on a tumor evolution prediction process, in strong link with the TRAIL funded project « MOD : Mathematical modeling of the response to antiangiogenic drugs via medical imaging ».

Scientific animation and training

The University of Bordeaux and schools are a breeding ground for future research. Benefiting from the multidisciplinary approach in Bordeaux, TRAIL works with the training actors at the University of Bordeaux and with partners, and supports a dynamic scientific animation program.

3.1 TRAIL scientific events in Bordeaux

Conferences

TRAIL teams invited 37 international speakers to give lectures in Bordeaux (see annex C.1 for details). For example, in 2016, 9 lectures were given : P Douek, A Kontush, A Obenaus, S Eskildsen, F Delmas, L Hirt, J Duarte, L Pellerin.

Scientific days

TRAIL research projects were presented by project leaders to the community during annual « intra-community scientific days », and during « work-package scientific meeting » (see annex C.2 for details).

Annual General Assembly

An annual General Assembly is organized each year, to present achievements, research projects, and the development strategy for the coming years to the Community.

Summerschools and thematic school

2 international summerschools were organized by the Community : « Connectomics, the wiring diagram of the human brain » in 2014, « Neuroepiomics » in 2015. A thematic school « Modulamag, contrast modulation in MRI » was organized in 2012 with the University of Mons, Belgium (see annex C.3 for details).

« We sincerely thank Cluster TRAIL for the precious support it has provided to the Neurepiomics summer school (September 28 – October 2, 2015), also generously supported by IdEx Bordeaux (as well as the Music for the Brain initiative). In this era of «omics», this fi rst summer school dedicated to the teaching of neuroepidemiology in large cohorts was highly appreciated by students and speakers, many of whom took part in all sessions. The imaging courses, given by internationally renowned speakers - Fabrice Crivello (Bordeaux), Myriam Fornage (Houston), Arfan Ikram (Rotterdam), Bernard Mazoyer (Bordeaux), Paul Thompson (Los Angeles), and Nicolas Vinuesa (Bordeaux) - were particularly appreciated. The sessions presented the new MRI markers of neurological disorders of the aged, the genome-wide association studies (GWAS) making it possible to identify the genes that predispose humans to brain structure alterations through MRI within international consortia (ENIGMA, CHARGE), the new-generation sequencing methods applied to the MRI markers of cerebral small-vessel disease, as well as the new epidemiological approaches to examining the issues of causality and mediation. These sessions also included a comprehensive interactive workshop. The Neurepiomics summer school is set to be held alternately in Bordeaux and Boston (2016). »

Pr Stephanie Debette,
Research Director,
U897 Center

Informing the Community

The TRAIL website (http://trail.labex.u-bordeaux.fr/en/) is dedicated to inform about the LabEx, about events and internal calls ; in addition, a newsletter is sent to each Member of the Community to highlight specific event/ information. The Website and the Newsletter are both in english ; the graphical chart is common to all communication media of the LabEx (see annex C.4 for details).

3.2 Partnerships with international scientific events

Specific partnerships were built with international scientific events.

Year	Scientific event	Thematics
2012	NGI	Neuron-glia interactions
2015	Euroanalysis (Bordeaux, Sept 2015)	Analytical chemistry
2015	KidMRI (Bordeaux, Oct 2015)	Functional MRI for renal parenchymal disease: Ready for clinical practice
2016	Aptamers in Bordeaux (Bordeaux, June 2016)	Aptamers biology, chemistry & technologie
2016	Congrès de la Section 28 du CNRS (Bordeaux, June 2016)	Pharmacology, bio-ingineering, imaging
2016	Cosine 6 (May 2016)	Medicine and digital
2016	ESUR (Bordeaux, Sept 2016)	European Symposium on Urogenital Radiology
2016	GECO57 (Ascain, Aug 2016)	Organic chemistry
2017	5e Ecole d'imagerie du Petit animal appliquée au Cancer (Bordeaux, June 2017)	Oncology preclinical imaging
2017	Aptamers in Bordeaux (Bordeaux, Sept 2017)	Aptamers biology, chemistry & technologie
2017	ERANET (Bordeaux, June2017)	Neuroimaging changes after acute brain injuries to evaluate the remote plasticity
2017	NeuroFrance 2017 (Bordeaux, May 2017)	Neurosciences
2017	SFRMBM (Bordeaux, March 2017)	MRI, MR spectroscopy

3.3 Links with the international Master of BioImaging

In collaboration with the University of Laval in Quebec and the University of Mons in Belgium, the Master of Bioimaging was launched in 2012. The objective is to master theoretical concepts and practical know-how of the main bioimaging techniques with all courses given in English (see annex C.5 for details).

62 students followed courses over the 2012-2016 period.

Scientific animation and training

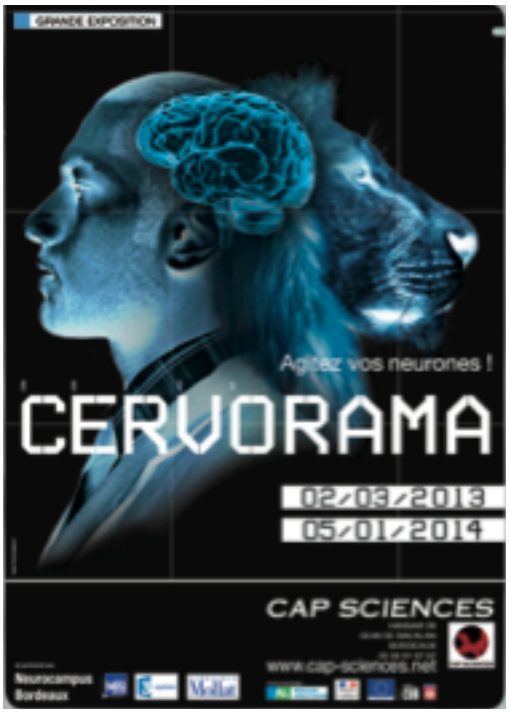
3.4 Links with the FLI network

The French Life Imaging (FLI) national infrastructure (Bordeaux, Grenoble, Lyon, Marseille, Paris) is reorganizing the educational programs for students and young researchers to make a national and international offer. TRAIL, as a member of FLI, participates to this program.

3.5 Knowledge dissemination to wide audience and general public

Several events have been set up to ensure knowledge dissemination to a large audience :

- TRAIL collaborated in 2013 on an exhibition called CERVORAMA which was organized by Cap Sciences Museum in Bordeaux. The exhibition showcased the uniqueness of the brain: brains of animals and humans, cognitive functions, memory, plasticity, 3D interactive presentation of brain anatomy, playing tricks on the brain. 62,000 people visited the exhibition in one year;
- TRAIL is working with Harvard Medical School on a spine project with crowd sourcing for large scale medical imaging postprocessing;
- Researchers involved in TRAIL projects, gave lectures on the following topics in partnership with Cap Sciences, with the ARSEP fundation, the « House for Science », and the « Collège de France »: Neuroimaging and cerebral plasticity, Brain imaging, Memory, Alcohol and cerebral modifications.



4/ Attractiveness

4.1 International academic partnership

Due to the multidisciplinarity of the TRAIL research portfolio, the TRAIL teams collaborate with numerous international academic partners throughout the world (see annex D.1 for details).

A total of 34 publications quoting TRAIL (38% of the total number of publications) has been produced with international partners.

Attractiveness

4.2 European projects

Since 2012, TRAIL teams have been involved in 7 european projects, increasing its international visibility :

- 2016: ERA-net NEURON-Trains ; COST Action ; IMI Beat-DKD;
- 2015: FLAG-ERA JTC Multilateral (Netherlands, France, Spain);
- 2014: ERA-net NEURON-CnsAflame (Germany, France, Sweden, Israel);
- 2013: ITN Marie Curie EDU-GLIA (Germany, UK, France, Sweden, Slovenia, Czech Republic, Israel);
- 2012: ITN Marie Curie-Pi-Net (Spain, France, UK, Germany, Sweden).

In 2016, one Member of the TRAIL Community was granted an ERC Starting for the ECSTATIC project («Electrostructural Tomography, Towards Multiparametric Imaging of Cardiac Electrical Disorders», Hubert Cochet).

Also, the LabEx TRAIL is member of the The European Institute for Biomedical Imaging Research (EIBIR, http://www.eibir.org/) since january 2016, that « aims to coordinate and support the development of biomedical imaging technologies and the dissemination of knowledge with the ultimate goal of improving the diagnosis, treatment and prevention of disease ».

4.3 Visiting Scholars and mobilities

TRAIL has been accredited by IdEx Bordeaux to welcome 7 international visiting professors since 2014:

- Pr Troels Skrydstrupi (Aarhus University, Copenhagen);
- Pr Charles Guttmann (University of Harvard, Boston);
- Pr Denis Parker (University of Utah, Salt Lake City);
- Pr Juan P. Bolanos (The Institute of Functional Biology and Genomics, Salamanca);
- Pr Anil Kumar Mishra (Institute of Nuclear Medicine and Allied Sciences, New Dehli);
- Pr Jing-Huei Lee (University of Cincinnati, Cincinnati);
- Pr André Obenaus (Loma Linda University, Loma Linda).

Outgoing mobility is supported through partnership between TRAIL teams and international universities :

- Clément Morgat : mobility to INMAS, India;
- Julien Jouganous : mobility to MacGhill University, Canada;
- Gisèle Clofent-Sanchez : mobility to the University of Melbourne, Australia;
- Thomas Tourdias : mobility to Stanford University, USA;
- Thomas Cornilleau : mobility to Aarhus University, Denmark;
- Sébastien Benzekry : mobility to Roswell Park Cancer Institute, USA.

Pr Thomas Tourdias,
Professor of Radiology and Medical imaging

« My work within the Richard M. Lucas Center for Imaging in Stanford (Brian Rutt team) allowed the development of very high fi eld Magnetic Resonance Imaging (7 Tesla MRI) for better exploration of the brains of patients with multiple sclerosis. In particular, we developed methods allowing the precise analysis of brain structures potentially aff ected by the disorder but poorly or not yet explored with standard MRI tools (1.5 or 3 Tesla), such as the cortex, thalamus and hippocampus. These new imaging methods provide more detailed information with respect to the patients' symptoms and could in the longer term allow closer tracking of the development of the illness to support therapeutic decision-making. I am currently engaged in active collaboration with Brian Rutt's team in Stanford and we share the MRI techniques that we use in our Bordeaux research. »

4.4 Recruitments

46 persons have been recruited by TRAIL research projects (see annex D.2 for details) :

- 18 post-doctoral fellows
- 14 doctoral fellows
- 10 engineers
- 4 technicians

The support of Cluster TRAIL enabled me to prepare a doctorate in neurosciences, obtained with the congratulations of the jury, on the role of the positioning of a cerebral infarct in the prediction of a patient's clinical course. Analyses were performed on a cohort of 428 patients having suff ered a cerebral infarct and admitted to the Pellegrin hospital. This research was published in an internationally renowned journal. TRAIL also fi nanced my travel to the CNI laboratory in Boston headed by Pr Charles Guttman. During my stay, I improved my skills in MRI image processing. The knowledge gained was subsequently used in 2 projects, Reactiv and Scicog.

Dr Fanny Munsch,
PhD in Neurosciences

4.5 Collaboration with industrials

Medical imaging is a highly competitive sector: it has daily clinical applications and it represents the most important health expense in the world and this huge market attracts many researchers and industrials.

TRAIL work-packages and research projects show the Ex-cellence of Bordeaux research in medical imaging but they are competing with major international research centers as well as industrial research. TRAIL objective is to define the right moment/Technology Readiness Level to transfer the result of research to industry, either through a proof of concept, or through animal experiment, or through clinical experiment.

21 companies have been involved in TRAIL research projects since 2011 through direct co-funding, human resources and free use of their products/equipments :

- AFFICHEM: drug design for oncology;
- BALT: endovascular treatment of intracranial aneurysms;
- BRUKER: imaging sequence development and magnetic particle imaging;
- CADESIS: database management for cohort imaging;
- GLAXOSMITHKLINE: preclinical oncology imaging and drug efficiency testing;
- IBA MOLECULAR: radiotracers development;
- IGT SA: HIFU development for oncology and cardiology;
- INTRASENSE: post processing for pulmonary imaging;
- LFB BIOTECHNOLOGIES: antibodies engineering;
- MERK SERONO: neuroinflammation clinical studies;
- MICROVENTION: endovascular treatment of intracranial aneurysms;
- NOVAPTECH: aptamer-based tools;
- PACIFIC BIOSCIENCES: human immunoglobulin sequen-cing;
- PENUMBRA: endovascular treatment of intracranial aneurysms;
- PHILIPS: sequence development;
- ROCHE: immunotherapy modeling;
- SANOFI: MRI/PET bioimaging markers for Alzheimer disease;
- SIEMENS: oncology imaging, HIFU development;
- SUPERSONIC IMAGING: imaging equipment prototyping;
- TEVA: support for neuroinflammation clinical studies;
- UNITHER: drug efficiency study.

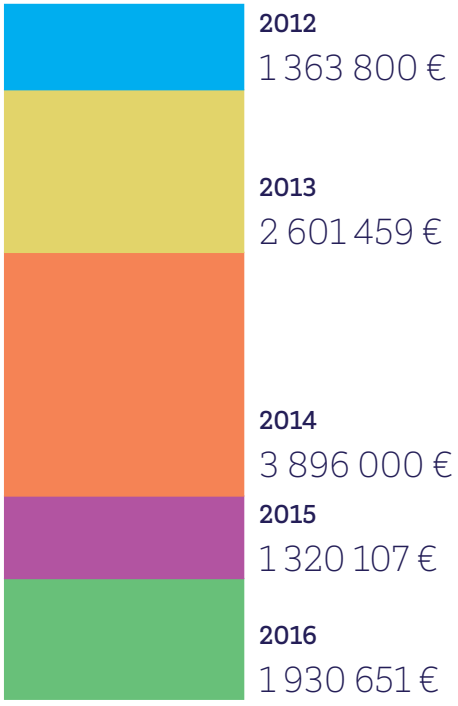
Attractiveness

Cancer Research and Clinical Center team

The company IGT (Image Guided Therapy) is based in the Gironde and produces High Intensity Focussed Ultrasound (HIFU) systems. It has been collaborating over the past few years with the UCAIR laboratory at the University of Utah in Salt Lake City, headed by Professor Dennis Parker. Together they have developed a prototype for MRI-guided HIFU for the treatment of breast tumours, which has been tested on animals with successful results. The platform proposed by IGT and UCAIR for breast tumour treatment was installed at the Institut Bergonié in October 2015 and will be used for a clinical protocol as soon as the required authorisation has been obtained (fi le pending). The Cluster TRAIL has enabled research on HIFU to be continued by funding a federative project.

4.6 Cofunding

TRAIL research projects leaders have reinforced their projects budgets with a total of 11,1M€ of cofunding, including 1,28M€ from private sector (see annex D.3 for details):



Total
11 112 017 €

Annex

Annex

A/ Governance

A.1 TRAIL main figures per year

			TOTAL	2011	2012	2013	2014	2015	2016
RESEARCH	RESEARCH PROJECTS	Number of new projects	34	5	9	6	2	5	7
		Number of new «emerging» projects	16	0	5	2	2	3	4
		Number of new «federative» projects	18	5	4	4	0	2	3
		Research budget	5 407 911 €	493 971 €	1 150 866 €	894 448 €	490 000 €	979 618 €	1 399 008 €
		Research budget for «emerging» projects	1 328 400 €		150 000 €	160 000 €	335 000 €	260 000 €	388 400 €
		Research budget for «federative» projects	4 114 511 €	493 971 €	1 000 866 €	734 448 €	155 000 €	719 618 €	1 010 608 €
		Number of medical thematics of TRAIL matrix covered by granted research projects	5 (100%)	2	3	4	4	4	5
		Number of WP of TRAIL matrix covered by granted research projects	7 (100%)	4	6	7	7	7	7
		WP1 budget	430 000 €		30 000 €	140 000 €		100 000 €	160 000 €
		WP2 budget	429 600 €		280 000 €	100 000 €			49 600 €
		WP3 budget	482 500 €	97 500 €		180 000 €	45 000 €	160 000 €	
		WP4 budget	1 017 800 €	119 000 €	250 000 €	60 000 €	45 000 €	345 000 €	198 800 €
		WP5 budget	1 626 233 €	179 971 €	311 036 €	100 000 €	300 000 €	344 618 €	390 608 €
		WP6 budget	650 000 €			180 000 €	35 000 €		400 000 €
		WP7 budget	806 778 €	97 500 €	279 830 €	134 448 €	65 000 €	30 000 €	200 000 €
		IMB budget	615 000 €			180 000 €			400 000 €
		INSERM U1049 budget	30 000 €		30 000 €				
		INSERM U1215 budget	770 654 €	130 000 €	281 036 €		100 000 €	59 618 €	200 000 €
		U1045 (CRCTB) budget	709 448 €			274 448 €	35 000 €	100 000 €	300 000 €
		UMR 5287 CNRS (INCIA) budget	748 400 €		280 000 €	30 000 €		240 000 €	198 400 €
		UMR 5296 (GIN) budget	412 330 €	97 500 €	249 830 €		65 000 €		
		UMR 5536 (RMSB) budget	1 713 079 €	147 471 €	310 000 €	380 000 €	245 000 €	480 000 €	150 608 €
		UMR5255 (ISM) budget	444 000 €	119 000 €		30 000 €	45 000 €	100 000 €	150 000 €
	SCIENTIFIC COMMUNICATION	Number of publications quoting TRAIL	89		1	7	14	24	43
		Number of publications showing an impact factor <5	57		1	5	10	17	24
		Number of publications showing an impact factor between 5 and 10	29			2	4	5	18
		Number of publications showing an impact factor >10	3					2	1
		Number of publications of WP1 projects	3					1	2
		Number of publications of WP2 projects	22			2	4	10	6
		Number of publications of WP3 projects	6			1	2	1	2
		Number of publications of WP4 projects	15		1	1	2	1	10
		Number of publications of WP5 projects	32			3	5	8	16
		Number of publications of WP6 projects	4					2	2
		Number of publications of WP7 projects	7				1	1	5
		Number of publications of EA IMOTION projects	2						2
		Number of publications of IMB projects	4					2	2
		Number of publications of INSERM U1215 (MAGENDIE) projects	19			1	4	5	9
		Number of publications of U1045 (CRCTB) projects	6					1	5
		Number of publications of UMR 5287 (INCIA) projects	13				3	1	9
		Number of publications of UMR 5536 (RMSB) projects	36			5	7	14	10
		Number of publications of UMR 5255 (ISM) projects	9		1	1		1	6
		Number of scientific communications during interna-tional events	94	0	0	9	18	27	40

A/ Governance

			TOTAL	2011	2012	2013	2014	2015	2016
TRAINIG ATTRACTIVENESS GOVERNANCE	SCIENTIFIC EVENTS	Number of supported scientific events	15	0	2	0	1	3	9
		TRAIL cofunding	84 900 €	- €	14 400 €	- €	15 000 €	19 000 €	36 500 €
	TRAIL EVENTS IN BORDEAUX	Number of» scientific days»	4	0	0	1	1	1	1
		Number of lectures by international speaker in Bordeaux	37	0	1	10	5	12	9
	MASTER BIO-IM.	Number of students	62	nd	14	15	10	11	12
	SCIENTIFIC COLLABORA-TIONS	Number of new academic international collaborations	33	5	14	4	2	1	7
		Number of new academic national collaborations	31	7	7	8	3	1	5
		Number of new european project (includ. ERC)	8	0	1	1	0	2	4
		Number of visiting scholars (Idex program)	7	0	0	0	3	2	3
		Number of outgoing mobilities	6	0	0	1	0	4	1
	COFUNDING	Budget	11 112 017 €	- €	1 363 800 €	2 601 459 €	3 896 000 €	1 320 107 €	1 930 651 €
		Cofunding budget/TRAIL research budget	205%	0%	119%	291%	795%	135%	138%
	INDUSTRIAL VALORIZATION	Number of patents	10	0	0	0	7	2	1
		Number of recordings at the Software Protection Agency	4	0	0	0	0	0	4
		Private cofunding	1 133 559 €	- €	40 000 €	511 459 €	520 000 €	62 100 €	145000
		Number of industrials in link with TRAIL	21	5	9	3	1	3	0
		Number of new collaborations with industrials	33	5	10	6	1	4	7
	RECRUITMENTS (FUNDED BY TRAIL)	Number of post-doctoral fellowships	18	0	1	1	5	4	7
		Number of doctoral fellowships	14	0	3	0	1	4	6
		Number of engineers	10	0	0	1	3	2	4
		Number of technicians	4	0	0	0	1	1	2
		Number of administrative staff	2	1	1	0	0	0	0
		Total number of recruitments	48	1	5	2	10	11	19
		% of research budget dedicated to human resources	69%	76%	47%	64%	75%	83%	78%
	BUDGETS AND GOVERNANCE MEETINGS	Number of Steering Committees	49	4	9	10	8	9	9
		Number of Scientific Advisory Boards	1	0	0	0	0	1	0
		Number of Boards of Trustees	2	0	1	0	0	0	1
		Number of Annual General Assemblies	6	1	1	1	1	1	1
		Number of audits by the national research agency	1	0	0	0	0	1	0
		Number of CorePartners - Number of teams	7-10	8-8	8-8	8-8	8-8	8-8	7-10
		Number of persons in the community	260	240	240	240	240	240	260
		Global TRAIL budget	6 675 338 €	534 671 €	1 301 511 €	1 001 185 €	611 879 €	1 572 489 €	1 653 603 €
		Research budget	5 407 911 €	493 971 €	1 150 866 €	894 448 €	490 000 €	979 618 €	1 399 008 €
		Budget dedicated to governance, training, MRI time for the Community	1 267 427 €	40 700 €	150 645 €	106 737 €	121 879 €	592 871 €	254 595 €

A.2 The Community

The Community is composed of 260 persons : researchers, clinicians, Post-docs, PhD students, engineers working on complementary themes.

Position	Number of persons
Researchers/clinicians	121
Postdoctoral fellows	44
Doctoral fellows	42
Engineers	40
Technicians	13
TOTAL	260

A.3 Steering Committee

STEERING COMMITTEE					
Function	Units	Director	Thematics	Team (N=10)	Representative (N=16)
LabEx Director					V Dousset
CorePartner representatives	CRCTB	R Marthan	Bronchial modelinglin	P Berger	P Berger
			Cardiac Electrophysiology cardiaque	M Haïssaguerre	H Cochet
	EA 7435 IMOTION	F Couillaud	Molecular imaging and innovative therapies in oncology	F Couillaud	F Couillaud
	IMB	JM Couveignes	Scientific calculation	T Colin	O Saut
	INCIA	JR Cazalet	Neuroimaging and human cognition	I Sibon & J Swendsen	I Sibon
			Brain molecular imaging	J Badaut & P Zanotti - Fragonara	J Badaut
	ISM	E Fouquet	Molecular imaging and photonic	M Blanchard-Desce	Y Cremillieux
			Catalysis, Synthesis and Health	E Fouquet	E Fouquet
	RMSB	JM Franconi	Center for magnetic resonance of biological systems	JM Franconi	AK Bouzier-Sore
	U1215	PV Piazza	Glia-neuron interactions	B Brochet	B Brochet
Thematics representatives	Neurology				B Hiba
	Oncology				J Palussiere
	Cardiology				M Montaudon
	Pneumology				G Dournes
	Nephrology				N Grenier

WORK-PACKAGES COORDINATORS (N=7)	
WP1, Interventional imaging and MRI guided HIFU	B Quesson
WP2, New sequences	S Miraux
WP3, DNP	E Thiaudiere
WP4, Tracers & contrast agents	M Blanchard-Desce and P Fernandez
WP5, Biological Bio-imaging markers	G Clofent-Sanchez
WP6, Mathematic simulation and modeling	T Colin
WP7, Cohort imaging methodology	F Laurent

A/ Governance

A.4 Mid-period audit by the ANR (2015)

■ 1. Noteworthy productions

› 1.1. Outstanding progress regarding research

The TRAIL (Translational Research and Advanced Imaging Laboratory project) is an initiative based on internationally competitive research teams located in the Bordeaux area. TRAIL is articulated around seven work packages addressing, originally, five major themes (Note: Nephrology will probably be canceled). The launch of 23 projects has a strong effect on the 6 partners networking and build a very promising multidisciplinary research environment. Indeed, the Panel was most impressed by the capability of the leaders to forge a large, functioning collaborative network. By the end of 2014, achievements were 8 patents, 17 publications acknowledging TRAIL and 190 peer reviewed publications, but the latter gave no credit to TRAIL funding. The Panel was disappointed in the scientific output from the collaborations, which tended to be published in specialist, low impact journals.

› 1.2 Striking progress in other "Labex" fields

a. Formation
In 2012 a international bio-imaging master was started. The master is a joint venture of LabEx TRAIL and BRAIN and take benefit of international support from University of Laval (Quebec) and University of Mons (Belgium). TRAIL also successfully support mobility for international collaboration. TRAIL set up a summer school on neuro-imaging and attracted 26 international renown speakers . 11 international speakers were invited by the TRAIL community. TRAIL belongs to the French Life Imaging (FLI).

b. Valorization
8 patents were filled and 15 industrial are involved in TRAIL projects.

c. International (outreach, attraction, networking...)
TRAIL does have international collaboration running. However this aspect needs to be further reinforced to raised TRAIL profile outside Bordeaux.

■ 2. Added-value resulting from labelling and funding as a "Laboratoire d'Excellence"

The TRAIL labeling helped to raise 2.5 more co-funding (public as well as private). TRAIL initiative results in the building of an efficient and high level multidisciplinary research between the existing laboratories.

■ 3. Main weaknesses

› 3.1. Main weaknesses that might require corrective actions regarding the research performed in the "Labex"

The TRAIL initiative is too much a Bordeaux initiative. International as well as national collaboration should be enhanced. Co-supervision of PhD as well as reinforcing mobility (in both directions) should be considered. There is a great danger in lack of focus with the current strategy of supporting such a wide range of projects. At some point, hard decisions must be made to prioritise funding to achieve high level scientific outputs.

› 3.2 Main weaknesses that might require corrective actions regarding other fields of the "Labex"

a. Formation
The TRAIL initiative should increase the academic exchange (both direction) with focus on PhD activity.

b. Valorization
Valorization is developing well but could still be improved. It is essential that exploitation of filed patents is actively pursued.

c. International (outreach, attraction, networking...)
The international networking is good but need to be further developed especially at EU level.

■ 4. "Labex" contribution to structuring the gathered scientific strengths (governance, synergy, common scientific programming, visibility...)

TRAIL successfully built up a multidisciplinary Bordeaux research network in advanced medical imaging. The governance is well organized. However, the newly hired general manager must solve the issues raised by the scientific advisory board regarding over complex administrative processes and project governance. Streamlining of these processes is important to keep the partners fully engaged with TRAIL.

■ 5. Beyond scientific results specifically obtained by the "Labex", give an assessment on its contribution to the development, outreach and overall visibility of the concerned institutions and of the corresponding site.

The panel consider that the Labex support lead to the creation of a strong consortium in advanced imaging in the Bordeaux area. In the mid term TRAIL initiative, thank to an adequate selection of projects and partnership (academic and industrial, nationally and internationally) may reach an international visibility and recognition. With such a profile, the TRAIL project the panel expect a step change in increased academic output.

■ 6. Overall opinion and recommendations

Overall the panel was very impressed by the scientific progress reported by the consortium: it has successful built an impressive collaborative network, potentially positioned to deliver in the future. The panel recommends TRAIL to balance the continuation of existing project with the start of new ones. The panel recommend to further prioritize risky projects focusing on unmet medical needs, at the expense of existing projects that may not come to fruition. Such 'risk projects' need not be peer reviewed but they should be selected by the steering committee and have a clear interdisciplinary vision. It is important that TRAIL select projects that can have high international impact, as currently their output is unsatisfactory. There is clearly a difficult job to be done in balancing the portfolio of diverse research themes so that in the next period a step change of increased publication quality is achieved. On the valorization perspective, the panel recommends to further improve the industrial collaboration and to evaluate how some of the ongoing /foreseen developments may lead to creation of start-up(s). The goal to have a strong local industry active in the field of advanced imaging should be one of TRAIL long term goal. The panel also recommends TRAIL to develop national, outside the Bordeaux area, as well as international collaborations. PhD exchange (both directions) and/or shared PhD could be a way to start such collaborations. The panel recommends to further develop the summer school programs and, if possible, to collaborate with other LabEx similar activities (e.g. CAMI). » International jry from the french National Research Agency, June 2015.

B/ Research achievements

B.1 Research portfolio : project abstracts and publications

B.11 Work package "interventional imaging and MRI guided HIFU"

HIFU

High-Intensity Focused Ultrasound

- Oncology
- 2012
- Klaus Petry, the "Neuroinflammation, imaging and therapy of multiple sclerosis" Inserm unit U1049
- TRAIL funding: 30 000 €

Passage of the blood brain barrier (BBB) is essential for effective drug delivery into the central nervous system. High-Intensity Focused Ultrasound (HIFU) has shown promising for non-invasive and focal opening of the BBB. Very limited, however, is the understanding of the underlying cellular and molecular mechanisms at the BBB, in particular of the endothelial cells being involved in such HIFU induced opening and eventually induced unwanted side effects. By in vitro studies of the BBB model (hCMEC/D3 cell line) under HIFU we will investigate the cellular and molecular dependent transports (clathrin, caveolin, tight junctions) and their specific inhibitions. In vivo studies of focally HIFU induced BBB alteration and histopathological evaluation and molecular expression studies of endothelial cells will validate the defined activated cellular and molecular transports. Histopathological studies will evaluate eventual non desired side effects of BBB opening and in adjacent CNS parenchyma due to the focal HIFU application. A portable HIFU system in application to small cell cultures and in vivo studies has been locally developed in partnership with Image Guided Therapy SA (Pessac, France) and in collaboration with TRAIL.

MRGHIFU

Methodological developments for preclinical and clinical applications of MR guided HIFU

- Oncology-cardiology
- 2013
- Bruno Quesson, the Bordeaux Cardio-Thoracic Research Centre (CRCTB, U1045)
- TRAIL funding: 400 000 €

The possibility to locally deposit thermal and mechanical energy in a non-invasive way with focused ultrasound (High Intensity Focused Ultrasound - HIFU) has opened new possibilities for the development of innovative therapies with improved reliability and reduced associated trauma (Ter Haar et al, 2012). In the last decade, real-time imaging (ultrasound (US) and Magnetic Resonance (MR)) methods have been developed to characterize ultrasound propagation in living tissues and to measure and control the local heat deposition. The aim of the present project is to develop new methods for MR guided HIFU by exploiting the hardware platform installed in Bordeaux. This project builds on the deep knowledge in real time guidance of MR guided HIFU effects to reinforce fundamental research in cardiology and oncology and to facilitate translation toward clinical application. This proposal associates several academic teams (INSERM, CNRS) in Physics and Biology, clinicians (Anti Cancer Center Bergonié), one international collaborative team (Univ. Salt lake City) and receives the support of a local company specialized in MR guided HIFU instrumentation and methods (Image Guided Therapy SA). The project is structured in four work packages, including methodological developments of MR monitoring methods (WP 1), new HIFU sonication strategies (WP 2), in vivo characterization on small animal models of the interaction between HIFU and biological tissues (WP 3) and preclinical evaluation and optimization of a dedicated breast MRgHIFU platform (WP 4). This project receives important co-financing and requests funding for additional human resources. The objective is to improve the synergy between the different scientific objectives of the research community (fundamental research, cardiology and oncology) and should benefit to other research teams for future applications. The direct implication of a local company (IGT SA) reinforces the immediate collaboration between each research team and aims to facilitate technological transfer and emergence

of new products and applications (each site being equipped with similar MRI scanners (Siemens) and all HIFU devices being designed by IGT SA), with the aim to shorten the time scale between technical advances, fundamental research and clinical applications.

Publications quoting TRAIL:

- Detection of Brain Tumors and Systemic Metastases Using NanoLuc and Fluc for Dual Reporter Imaging. C. Germain-Genevois, O. Garandeau, F. Couillaud. Mol Imaging Biol, 2015;
- Improved Cardiac Magnetic Resonance Thermometry and Dosimetry for Monitoring Lesion Formation During Catheter Ablation, Valery Ozenne, Solenn Toupin, Pierre Bour, Baudouin Denis de Senneville, Matthieu Lepetit-Coiffe, Manuel Boissenin, Jenny Benois-Pineau, Michael S. Hansen, Souheil J. Inati, Assaf Govari, Pierre Jais, and Bruno Quesson, Magnetic Resonance in Medicine, Jan 2016;
- Non-invasive cardiac pacing with image-guided focused ultrasound, Fabrice Marquet, Pierre Bour, Fanny Vaillant, Sana Amraoui, Rémi Dubois, Philippe Ritter, Michel Haïssaguerre, Mélèze Hocini, Olivier Bernus & Bruno Quesson, Nature Scientific Report, Oct 16.

B.12 Work package "new sequences"

HRDTI

High Resolution DTI method

Neurology	Bassem Hiba, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
2012	TRAIL funding: 130 000 €

Despite its clinical strength, Diffusion Tensor Imaging (DTI) inherently suffers from a limited signal to noise ratio which leads to a low spatial resolution. The limited resolution (2-3 mm) of DTI introduces large partial volume effects which could limit the accuracy of diffusion parameter assessment for small structures of brain (cortical gray matter and small tracks of white matter) and mask changes of diffusion parameters in small pathological lesions. We have developed a high resolution (HR) DTI strategy, based on an optimal acquisition method and on new denoising and interpolation post-processing algorithms. This very promising approach has provided HRDTI data with a submillimeter isotropic resolution (0.4 mm). The aim of this proposal is to optimize the acquisition and post-processing methods and to validate our HR-DTI approach at 3T.

Publications quoting TRAIL:

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- MRI Noise Estimation and Denoising Using Non-local PCA, J. V. Manjon, P. Coupé, A. Buades. Medical image analysis, 22(1): 35-47, 2015;
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Research achievements

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- An Optimized PatchMatch for Multi-scale and Multi-feature Label Fusion. R. Giraud, V-T. Ta, N. Papadakis, J. V. Manjón, D. L. Collins, P. Coupé and ADNI. NeuroImage 2015;
- Detection of Alzheimer's Disease Signature in MR Images Seven Years Before Conversion to Dementia: Toward an Early Individual Prognosis. P. Coupé, V. S. Fonov, C. Bernard, A. Zandifar, S. F. Eskildsen, C. Helmer, J. V. Manjón, H. Amieva, J-F. Dartigues, M. Allard, G. Catheline, D. L. Collins, and ADNI. Human Brain Mapping, 2015;
- Non-local means inpainting of MS lesions in longitudinal image processing, Nicolas Guizard*, Kunio Nakamura, Pierrick Coupé, Vladimir S. Fonov, Douglas L. Arnold, D L. Collins, Frontiers In Neuroscience, nov 2015;
- Anatomically Constrained Weak Classier Fusion for Early Detection of Alzheimer's Disease. Mawulawo Komlagan, Vinh-Thong Ta, Xingyu Pan, Jean-Philippe Domenger, D. Louis Collins, Pierrick Coupé, and the Alzheimer's Disease Neuroimaging Initiative. Machine Learning in Medical Imaging, pages 141-148, 2014;
- Optimized PatchMatch for Near Real Time and Accurate Label Fusion. Vinh-Thong Ta, Rémi Giraud, D. Louis Collins, and Pierrick Coupé. MICCAI'14, 105-112, 2014;
- Collaborative patch-based super-resolution for diffusion-weighted images. Pierrick Coupé, José V. Manjón, Maxime Chamberland, Maxime Descoteaux, Bassem Hiba. NeuroImage 83 (2013) 245–261;
- Diffusion weighted image denoising using overcomplete local PCA. José V. Manjon, Pierrick Coupé, Luis Concha, Antonio Buades, D. Louis Collins, Montserrat Robles. PLoS One Sept 2013,Volume 8, Issue 9.

MDMRI

Methodological Developments in High Spatial/Angular-resolution DTI for ex-vivo validation of tractography

■ Neurology	■ Bassem Hiba, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
■ 2016	■ TRAIL funding: 49 600 €

Tractography based on diffusion-MRI is a unique technique to analyze non-invasively the microstructure and anatomical connectivity of brain white matter. This technique is widely used in neuroscience and has a high potential for neurosurgery, but still needs to be optimized and validated. To date the principal study that has examined the capacity of tractography to capture the connectivity revealed by tract tracing showed very poor correlation over medium to long distances [4](Van den Heuvel MP. et al., 2015 Human Brain Mapping 36 (8) : 3064-75). That study looked at the correlation of tract tracing data from the Kennedy lab (Markov N. et al., Cerb Cortex 2014) with dMRI data from different brains. Because there is an order of magnitude difference in connectivity weight for a given connection between individual brains we hypothesize that the correlation can be much improved by carrying out the tractographic measure and the tracing experiments in the same brain as in this proposal. The group of Hiba has developed a high sensitivity diffusion-MRI (dMRI) pulse sequence, based on a segmented 3D-EPI (Echo-Planner Imaging) sampling of Fourier space. We used this pulse sequence to acquire high b-value (up to 8000 s/mm2) diffusion images of a fixed macaque brain at 7 Tesla. The obtained images were artefact free (free of ghosting, eddy-currents and distortion artifacts) and with a very high spatial resolution (up to 300 microns isotropic). The application of a dedicated superresolution post-processing (Coupé et al. Neuroimage, 2013) on resulting data allowed to get HARDI (High Angular Resolution Diffusion Imaging) data of 150 microns of resolution. To our knowledge, such whole brain high quality data has never been achieved before. The methodology we have developed and the quality of resulting data meet all necessary conditions to perform precise tractography, and consequently, to optimize and validate the tractography by comparison with tract-tracing techniques.

These methodologies and resulting data should also be useful to provide a better knowledge of the precise white matter anatomy and connectivity in the macaque monkey brain, and consequently in the human brain. The objectives of this proposal are to:

1) Achieve ex-vivo very high resolution HARDI data in 4 specimens of macaque, and to optimize and validate advanced methods of tractography by comparing their results with those of tract-tracing using retrograde transport of fluorescent tracers (Markov et al., Cerebral Cortex 2014) performed in the same animal. Such validation has never been done before. Tractography methods, which will be applied in this project, Particle filtering

tractography (PFT) with anatomical priors (Girard et al. NeuroImage; 2014) combined with recent surface-enhanced tractography (St-Onge et al. Proceeding of ISMRM, Toronto, 2015), which is more robust to the gyral bias, were published by the group of Descoteaux;

2) Implement oscillating diffusion gradients on the 3D-DTI pulse sequence in order to achieve diffusion MRI data with variable diffusion times. The use of oscillating magnetic field gradients to encode water molecule diffusion in tissues allows a very short diffusion time and thus a better estimate of axon caliber. In the proposed project, an emerging strategy of tractography taking into account the axon caliber, ax-tract (Girard et al. Processing in Medical Imaging, IPMI, 2015) will also be optimized and validated in comparison with tract-tracing and other histological analysis of the 4 macaque brains. Finally, the obtained data will be made available to the community to carry out studies aiming to compare and optimize tractography algorithms and to increase the anatomical knowledge of the white substance in the macaque monkey brain and consequently in the human brain.

NEWFISP

improving MRI resolution to correctly MRI-diagnose cardiac pathologies and metastases

- Cardiology
- 2012
- Sylvain Miraux, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- TRAIL funding: 250 000 €

The goal of this project is: 1) to define the methods to perform MR images with high space and time resolutions, that would provide more quantitative data and thus more information at a local and at a whole-body level, and more adapted to patient imaging. 2) in the short and medium term, and in interaction with the IHU teams, to transfer the breakthrough developed by the RMSB cardio-vascular imaging team from small-animal to human, in order to correctly diagnose cardiac pathologies and accurately guide the therapies. 3) in medium and long term, and in interaction with the oncologists at Bergonie Institute, to develop original approaches to early diagnose metastases by MRI. This project is based on the development and improvement of the MR (b)SSFP sequence (fully balanced Steady State Free Precession). This sequence is already performed on an everyday basis at high magnetic field (4.7T, 7T and 9.4T) at the RMSB. This sequence was also adapted and optimized at clinical field (1.5T and 3T) by one of the co-author of this project. The strength of the development and optimization would allow the use of this sequence on small animals for preclinical studies on pathological models, and also on human to apply this sequence in clinical setting.

Publications quoting TRAIL:

- Free-breathing 3D diffusion MRI for high-resolution hepatic, metastasis characterization in small animals, Emeline J. Ribot, Aurelien J. Trotier, Charles R. Castets, Benjamin Dallaudiere, Eric Thiaudiere, Jean-Michel Franconi, Sylvain Miraux, Clin Exp Metastasis, Nov 2015;
- Fast and robust 3D T1 mapping using spiral encoding and steady RF excitation at 7T: application to cardiac manganese enhanced MRI (MEMRI) in mice. C. R. Castets, E. J. Ribot, W. Lefrançois, A. J. Trotier, E. Thiaudière, JM Franconi and S. Miraux. NMR in Biomedicine, mars 2015;
- Positive contrast high-resolution 3D-cine imaging of the cardiovascular system in small animals using a UTE sequence and iron nanoparticles at 4.7, 7 and 9.4 T, A. J. Trotier, W. Lefrançois, K. Van Renterghem, JM Franconi, E. Thiaudière and S. Miraux, Journal of Cardiovascular Magnetic Resonance (2015);
- Water Selective Imaging and bSSFP Banding Artifact Correction in Humans and Small Animals at 3T and 7T, Respectively; E. J. Ribot, D. Wecker, A. J. Trotier, B. Dallaudière, W. Lefrançois, E. Thiaudière, JM Franconi, S. Miraux, PLOS ONE, 2015;
- Self-gated bSSFP sequences to detect iron-labeled cancer cells and/or metastases in vivo in mouse liver at 7 Tesla. E. J. Ribot, T. J. Duriez, A. J. Trotier, E. Thiaudiere, JM Franconi, and S. Miraux. J Magn Reson Imaging. June 2014;
- Fast 3D Ultrashort Echo-Time Spiral Projection Imaging Using Golden-Angle: A Flexible Protocol for In Vivo Mouse Imaging at High Magnetic Field; Charles R Castets, William Lefrançois, Didier Wecker, Emeline J Ribot, Aurelien J Trotier, Eric Thiaudiere, Jean-Michel Franconi, and Sylvain Miraux*, Magnetic Resonance in Medicine, May 2016;
- USPIO-Enhanced 3D-Cine Self-Gated Cardiac MRI Based on a Stack-of-Stars Golden Angle Short Echo Time Sequence: Application on Mice With Acute Myocardial Infarction, Aurelien J. Trotier, PhD, Charles R. Castets,

Research achievements

MSc, William Lefrancois, PhD, Emeline J. Ribot, PhD, Jean-Michel Franconi, PhD, Eric Thiaudiere, PhD, and Sylvain Miraux, PhD*, Journal of Magnetic Resonance Imaging, jan 2016;

- Time-resolved TOF MR angiography in mice using a prospective 3D radial double golden angle approach. A. J. Trotier, W. Lefrançois, E. J. Ribot, E. Thiaudiere, JM Franconi, and S. Miraux. Magn Reson Med. 2014 Mar 10.

B.13 Work package "DNP"

ONCOFLUX

Metabolic flux MR imaging in tumors

- Oncology
- Yannick Cremillieux, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2013
- TRAIL funding: 240 000 €

Most tumor cells are characterized by abnormal metabolic pathways to generate energy (as exemplified in the well-known Warburg effect) and to sustain enhanced cell proliferation. This disturbed metabolism is a key hallmark of tumor cell aggressiveness and as a result of prognostic in patients. Importantly, the cancer cell metabolism can vary in time and be highly heterogeneous in a given tumor. Until recently, no single imaging technique was able to provide non-invasive measurements of metabolic fluxes with sufficient spatial resolution and sensitivity. However in the last decade, a new MR imaging tool based on hyperpolarization of C13-labelled metabolites has emerged as a highly sensitive non-invasive metabolic imaging technique. The UMR 5536 is equipped with a unique DNP (Dynamic Nuclear Polarization) apparatus able to dramatically enhance (5 orders of magnitude) the sensitivity of detection of hyperpolarized metabolized substrates with MRI.

The research program ONCOFLUX will aim at the detection and grading of malignant tumors in brain and lungs in animal models, and will focus on the investigation and quantification of the metabolic fluxes in vivo in these tumors. Besides, this research program will establish standardized hyperpolarization procedures and MRS/MRI protocols for in vivo metabolism investigation in cardiac, kidneys or brain applications.

Publications quoting TRAIL:

- MR imaging, targeting and characterization of pulmonary fibrosis using intra-tracheal administration of gadolinium-based nanoparticles, Nawal Tassali, Andrea Bianchi, François Lux, Gérard Raffard, Stéphane Sanchez, Olivier Tillement and Yannick Crémillieux, Contrast Media and Molecular Imaging, May 2016;
- In vivo online magnetic resonance quantification of absolute metabolite concentrations in microdialysate, Stefan Glöggler, Silvia Rizzitelli, Noël Pinaud, Gérard Raffard, Vanessa Zhendre, Véronique Bouchaud, Stéphane Sanchez, Guillaume Radecki, Luisa Ciobanu, Alan Wong, Yannick Crémillieux, Nature Scientific Reports, Nov 2016.

TRAILDNP

in vivo DNP in mice at 0,2T

- Neurology
- Eric Thiaudiere, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2011
- TRAIL funding: 242 500 €

The UMR 5536 is nowadays developing an unique double resonance modality, using electron spin resonance for enhancing MRI signal by dynamic polarization. This modality is now running in living mice, with clear contrast enhancement brought by the addition of nitroxides. By the same way, brain tumor locations was revealed by passive retention of free radicals at the tumor site. The proposal aims at hiring a PhD student for improving the method in order to provide high spatial and time resolutions. The work will consist in sequence developments, experiencing animal models and, if possible, hardware developments. The ultimate goal is to perform in vivo DNP-MRI to reveal disease-induced protease activity with chemically designed nitroxides provided by partners.

Publications quoting TRAIL:

- Enzymatically Shifting Nitroxides for EPR spectroscopy and Overhauser-Enhanced Magnetic Resonance Imaging, G. Audran, L. Bosco, P. Bremond, JM Franconi, N. Koonjoo, S. Marque, P. Massot, P. Mellet, E. Parzy, and E. Thiaudiere, Angew. Chem. 2015, 127, 1–7;
- In vivo Overhauser-enhanced MRI of proteolytic activity. Koonjoo N, Parzy E, Massot P, Lepetit-Coiffé M, Marque SR, Franconi JM, Thiaudiere E, Mellet P. Contrast Media Mol Imaging. 2014 Sep;9(5):363-71;
- Alkoxyamines: toward a new family of theranostic agents against cancer. Moncelet D, Voisin P, Koonjoo N, Bouchaud V, Massot P, Parzy E, Audran G, Franconi JM, Thiaudière E, Marque SR, Brémond P, Mellet P. Mol Pharm. 2014 Jul 7;11(7):2412-9;
- Overhauser-enhanced MRI of elastase activity from in vitro human neutrophil degranulation. E. Parzy, V. Bouchaud, P. Massot, P. Voisin, N. Koonjoo, D. Moncelet, J.M. Franconi, E. Thiaudiere, and P. Mellet, PLoS One. 8(2) 2013.

B.14 Work package "tracers and constrast agents"

FITTING

18F-Bioorthogonal probe for imaging traumatic brain injury glycol-biomarkers

- Neurology
- Frederic Friscourt, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2016
- TRAIL funding: 48 800 €

Traumatic brain injury (TBI) is a major public health issue and represents the leading cause of disability and death in Europe including France among young adults and children. Unfortunately, mild TBI is highly difficult to detect clinically using traditional neuroimaging techniques. Therefore, there is an important societal need to have new biomarkers to follow over the long-term the evolution of the injury after the initial trauma.

In this context, the surfaces of eukaryotic cells are covered with complex glycans that participate in a variety of physiological processes, including cell adhesion and cell-cell interactions. In the brain, polysialic acid (PSA) conjugates have been identified as key players in health of the nervous system. Imaging PSA glycoconjugates would deepen our understanding of cell surface neuroglycans functions and allow us to follow brain remodeling overtime due to traumatic brain injury and lead to potential novel diagnostic tools.

Imaging complex glycans have been historically a challenge due to the lack of specific biochemical tools. Recently, the metabolic oligosaccharide engineering (MOE) technology combined with bioorthogonal chemical ligations has elegantly allowed the visualization of various glycoconjugates in living cells.

The project aims at: 1) validating that PSA can be used as a TBI biomarker using the MOE technology and 2) in order to enable in vivo detection of PSA (translational application), a radio-bioorthogonal probe will be developed for PET imaging.

IMMELAPT

SPECT molecular Imaging and optimized apatmers for tumor detection

- Oncology
- Jean-Jacques Toulme, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2012
- TRAIL funding: 250 000 €

The ImMelApt project takes advantage of the potential of aptamers for recognizing a target of interest and aims at bringing an innovative answer to the need for imaging tumors in vivo. Starting from an aptamer we previously raised against the human MMP-9 -a protein that is overexpressed in tumors and is capable of degrading extra cellular matrix components, thus permitting cancer cell migration- we will i) synthesize and characterize several derivatives of this aptamer, ii) convert them into imaging probes, with different modalities, iii) image human melanomas ex vivo and iv) undertake in vivo experiments in animal model. The perspective of this project is the design of tools for detecting and monitoring human tumors, using SPECT molecular imaging.

Research achievements

Publications quoting TRAIL:

- Ex Vivo and In Vivo Imaging and Biodistribution of Aptamers Targeting the Human Matrix MetalloProtease-9 in Melanomas, David Kryza*, Frédéric Debordeaux, Laurent Azéma, Aref Hassan, Olivier Paurelle, Jürgen Schulz, Catherine Savona-Baron, Elsa Charignon, Pauline Bonazza, Jacqueline Taleb, Philippe Fernandez, Marc Janier, Jean-Jacques Toulmé, PlosOne, Feb 2016.

NANOMULTIMAG

Smart multimodal nanoprobes for MRI/MPI/NIRF imaging with magneto/optical contrast agents for atheroma plaque targeting

- Oncology
- Mireille Blanchard-Desce, the Institute of Molecular Sciences (ISM, UMR5255)
- 2016
- TRAIL funding: 150 000 €

The need to combine morphological and functional information at a micrometric scale has become of great concern in the medical field. We propose to develop nanometric multimodal probes, based on magneto and optical contrast agents, for Magnetic Particle Imaging/Magnetic Resonance Imaging and Near Infrared Fluorescence, for atheroma plaque targeting.

The originality of the project is multifaceted :

› It is based on a multidisciplinary approach, involving the interaction of experts in various fields, from chemistry and pharmacology to in vivo imaging;

› It exploits technologies of high potential: hyper-bright fluorescent probes, optimized ultrasensitive magnetic probes, biocompatible vehicles functionalized with innocuous target specific recognition, all of them generally at work independently;

› It focuses on the development of tools for an emerging powerful imaging methodology, with improved spatial resolution, with high potential in medical diagnosis and surgery.

This ambitious project may represent the starting point for the set-up of a technological progress of high importance in the medical field; it may open the route to a generalized methodology for early diagnosis and image guided navigation for minimal invasive surgery.

Publications quoting TRAIL:

- In vitro imaging of b-cells using fluorescent cubic bicontinuous liquid crystalline nanoparticles; V. Miceli, V. Meli, M. Blanchard-Desce, T. Bsaibess, M. Pampalone, P. G. Conaldi, C. Caltagirone, M. Obiols-Rabasa, J. Schmidt, Y. Talmon, A. Casu*, and S. Murgia*, RCS Advances, June 2016:
- Z-Shaped Pyrrolo[3,2-b]pyrroles and Their Transformation into p-Expanded Indolo[3,2-b]indoles, Rafał Stezycki,Marek Grzybowski, Guillaume Clermont, Mireille Blanchard-Desce* and Daniel T. Gryko*, Chemistry a European Journal, Feb 2016;
- Bright Electrogenerated Chemiluminescence of a Bis-Donor Quadrupolar Spirofluorene Dye and Its Nanoparticles; Haidong Li, Jonathan Daniel, Jean-Baptiste Verlhac, Mireille Blanchard-Desce,* and Neso Sojic*, Chemistry a European Journal, July 2016.

NEPMIP

NanoEmulsion Platform for Magnetic Particle Imaging

- Oncology
- Sylvie Crauste-Manciet, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2015
- TRAIL funding: 35 000 €

The objective of the present work is to develop a nanoemulsion platform dedicated for Magnetic Particles Imaging (MPI). This new tracer imaging modality is now at an exciting stage of development similar to where MRI was in the early 1980s. MPI can have extremely high contrast and sensitivity since it allows for directly detecting the magnetic nanoparticle without suffering from of any background tissue signal as compared with MRI. However SPIO nanoparticles with suitable sizes and functionalized coatings are key components for MPI. Therefore, the design of optimal tracer platforms will have to be done in a thoughtful way.

The original nanoemulsion systems we aim to develop will consist in a simple or double system (O/W or W/O/W) able to include iron magnetic particles for early diagnostic

of atherosclerotic plaques after a proper targeting process. First, we will synthesize the iron nanoparticles with a proper size for MPI detection following the procedure developed in our laboratory (1). Second, we will create a nanovesicular system including the iron nanoparticles with different controlled vesicular sizes obtained by using different surfactant compositions and different processes (high energy or self-emulsifying). Schematic representation of an expected W/O/W nanoemulsion system including iron nanoparticles is given in figure 1. Finally we will assess the capability of these different vesicular systems to be detectable by MPI in vitro, studying also the effect of grafting a specific antibody allowing for targeting atherosclerotic lesions.

PIAF

PET Imaging of Angiogenesis by 18F-RGD

- Oncology
- Eric Fouquet, the Institute of Molecular Sciences (ISM, UMR5255)
- 2011
- TRAIL funding: 164 000 €

The project will firstly establish the interest of the αvβ3 integrin imaging by PET imaging, by conceiving and achieving the synthesis of an original 18F-RGD radiotracer, then experimenting it on a murine tumoral model of melanoma. Secondly, in a perspective of « proof of concept », our molecular imaging project will consist in the validation of the 18F-RGD as a marker of the biological effect induced by therapies, inhibiting neoangiogenesis such as Dendrogenin A (a new and promising anti-tumoral recently discovered). A further objective will be to complete the pre-clinical evaluation of the molecule to bring it up to the clinical state and assess in situ its impact on the tumoral neovascularisation in order to select

Publications quoting TRAIL:

- General Last-Step Labeling of Biomolecule-Based Substrates by [12C], [13C], and [11C] Carbon Monoxide. Thomas Cornilleau, Hélène Audrain, Aude Guillemet, Philippe Hermange and Eric Fouquet. Org. Lett. 2015, 17, 354–357;
- Pd°-catalyzed methyl transfer on nucleosides and oligonucleotides envisaged as a PET tracer E. Fouquet et al. Molecules, 2013, 18, 13654-13665;
- [18F]Si-RiboRGD : the winning combination. From the design and the synthesis to the imaging of avb3 integrins in melanoma tumors. E Amigues, J Schulz, M Szlosek-Pinaud, P Fernandez, S Silvente-Poirot, S Brillouet, F Courbon and E Fouquet, ChemPlusChem 2012, 77, 345-349.

PRITOR

NeuroPeptide Receptors Imaging for TumOR Targeting

- Oncology
- Elif Hindie, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2013
- TRAIL funding: 90 000 €

Receptors of some regulatory peptides can be highly expressed in various human tumors, thus offering the opportunity of a specific molecular imaging with radiolabeled peptides. Advantageous pharmacological and pharmacokinetic properties as well as easy radiolabeling procedures make peptides attractive molecular tools for molecular imaging over antibodies and theirs derivates. The success encountered with the use of radiolabeled somatostatin analogs for imaging and targeted therapy of endocrine tumors that express somatostatin receptors is probably the first of a long list since multiple receptors are now recognized as potential targets.

This project will first compare the density and distribution of several neuropeptide receptors in human breast cancer in order to identify which one could be considered as the molecular target of highest interest.

The second part of the present molecular imaging project will consist in the pre-clinical evaluation of a [68Ga]-radiolabeled neuropeptide analog. Some analogs have already been synthesized by our teams.

Research achievements

Publications quoting TRAIL:

- A new class of radiopeptides for PET imaging of neuromedin-B receptor: 68Ga-ranatensin analogs, C. Morgat, R. Varshney, D. Vimont, C. Savona-Baron, C. Riès, C. Chanseau, S. Bertrand, A. K. Mishra, E. Hindié, P. Fernandez and J. Schulz, Med Chem Commun., April 2016;
- Dose Deposits from 90Y, 177Lu, 111In, and 161Tb in Micrometastases of Various Sizes: Implications for Radiopharmaceutical Therapy. Hindié E, Zanotti-Fregonara P, Quinto MA, Morgat C, Champion C., J Nucl Med. 2016 May;
- Comparison between Three Promising ß-emitting Radionuclides, (67)Cu, (47)Sc and (161)Tb, with Emphasis on Doses Delivered to Minimal Residual Disease. Champion C, Quinto MA, Morgat C, Zanotti-Fregonara P, Hindié E. Theranostics. 2016 Jun;
- Evaluation of 68Ga-DOTA-TOC PET/CT for the detection of duodenopancreatic neuroendocrine tumors in patients with MEN1, Clément Morgat & Fritz-Line Vélayoudom-Céphise & Paul Schwartz & Martine Guyot & Delphine Gay5 & Delphine Vimont & Jürgen Schulz & Joachim Mazère & Marie-Laure Nunes & Denis Smith & Elif Hindié & Philippe Fernandez & Antoine Tabarin, EJNMMI, jan 2016;
- Targeting neuropeptides receptors for cancer imaging and therapy: Perspectives with bombesin, neurotensin and neuropeptide-Y receptors. Morgat C, Mishra A.K, Varshney R, Allard M, Fernandez P, Hindié E. J Nucl Med. 2014;55(10);
- A phantom-based method to standardize dose-calibrators for new β+ emitters: 68Ga as demonstrative working example. Morgat C, Mazère J, Fernandez P, Buj S, Vimont D, Schulz J, Lamare F. Nucl Med Commun. 2014.

SUPSIFLU

Supported Silyl Fluorination

■ Oncology	■ Philippe Hermange, the Institute of Molecular Sciences (ISM, UMR5255)
■ 2013	■ TRAIL funding: 130 000 €

Positron Emission Tomography (PET) has become a powerful tool for medical diagnostic over the last decade, as illustrated by the extensive use of 2-desoxy-2-[18F]-fluoro-D-glucose for tumor imaging. However, fast and efficient last-step labeling by short-lived radionuclides still remains a challenging task with biomolecule based tracers. Indeed, they require smooth reaction conditions and optimized purification steps to obtain high radiochemical yield and purity. Developing new methodologies to overcome these issues, our team has been successfully able to label peptides and oligonucleotides for in vivo trials using nucleophilic fluorination of a silicon-based building block. As part of the TRAIL work package 4, our efforts are now focused on making this methodology adaptable to a simple automatized process. For example, pre-packed cartridges of the desired tracer would definitively allow a wider use of this labeling strategy for pre-clinical research by avoiding chromatography in purification steps. In this context, solid-phase supported tracers with a selective fluoride-triggered release could be perfect candidates. Despite these attracting advantages, no results on such tracers were reported to date, probably due to a lower reactivity of the very bulky di-tert-butylphenyl-silyl when is linked to a solid support. To overcome this effect, this emerging project proposes a positively charged leaving group (i.e. an imidazolium) that will facilitate the fluoride approach by salt metathesis. This moiety will be associated to the solid support and will ensure the selective release of fluorinated molecules (Scheme). Preliminarily studies with a non-supported model compound have validated the concept in term of synthetic feasibility and reactivity towards fluoride. Thus, further experiments are needed to optimize conditions in the case of a real biomolecule and to develop the promising supported version for 18F fluorination.

Publications quoting TRAIL:

- Gold-catalysed cross-coupling between aryldiazonium salts and arylboronic acids: probing the usefulness of photoredox conditions, Thomas Cornilleau, Philippe Hermange* and Eric Fouquet*, Chem Communication, July 2016.

TARGLIN

Targetting Glioblastoma with Nanoparticles, imaging siRNA targeting of glioblastoma using peptide-based nanoparticules

- Oncology
- Franck Couillaud, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2015
- TRAIL funding: 150 000 €

Even if chemotherapy constitutes the majority of treatments for most cancers, they are often limited by their lack of selectivity, targeting issues, rapid clearance and important side effects. In this context, new therapeutic agents specifically targeting molecular abnormalities of certain cancers have been developed. The identification of small interfering RNAs (siRNAs)2 and synthetic peptides3 open up the development of a new therapeutic approach. Although these molecules have great potential, their use remains limited by their low metabolic stability, selectivity and their inability to cross biological barriers. Therefore, since 10 years, "delivery" has become a major task for therapeutics, and more than 1/3 of the R&D budget of pharmaceutical companies has been dedicated to the design and optimization of delivery systems.

The development of peptide-based nanoparticles (PBN) is nowadays forwarded for intracellular transport of molecules of different nature and size. In the Montpellier laboratory several peptidic vectors have been developed (Pep-1, MPG, CADY) for the transfer of biomolecules from proteins to oligonucleotides. Moreover, the flexible and controllable nature of theses nanoparticles can serve as a basis for functionalization allowing specific targeting of certain organs or tissues.

The objective of this project is to develop peptide-based nanoparticles for addressing siRNAs targeting specific gene in glioblastoma and tumor microenvironment in a mouse xenograft model. In vivo imaging will be used to determine peptide-based nanoparticles bio-distribution, specific targeting and tumor growth reduction. In vivo data will be further confirmed up to sub cellular level by histological investigations.

PBN design, synthesis and labelling will be performed by the Montpellier team, in vitro assay will be performed both side by genetically modified cells lines engineered by the Bordeaux Team. Both in vivo imaging and histological studies will be performed in Bordeaux.

Publications quoting TRAIL:

- In Vivo Follow-up of Brain Tumor Growth via Bioluminescence Imaging and Fluorescence Tomography, Genevois C, Loiseau H and Couillaud F, International Journal of Molecular Sciences, Oct 2016.

B.15 Work package "biological bioimaging markers"

GMCOG

Grey matters! Toward a better understanding of grey matter alteration and cognitive deficit associated with multiple sclerosis

- Neurology
- Aurélie Ruet et Thomas Tourdias, the "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2016
- TRAIL funding: 200 000 €

Multiple sclerosis has been considered as a white matter disease for a long but the involvement of grey matter (GM) is now well recognized thanks to post-mortem data and progress with in vivo imaging. Nevertheless the mechanisms that trigger such GM alteration at the early stage of the disease are still poorly understood and reliable in vivo methods to quantify and to monitor the most eloquent GM areas in terms of cognitive impact are needed. In this federative translational project we will tackle these issues with a trans-disciplinary approach. In task 1, by using the animal model of multiple sclerosis, we aim at deciphering how activation of glial cells at the early stage of the disease can trigger alteration of hippocampal synaptic transmission, dendritic alteration, and in turn memory deficit. We will validate the ability of advanced in vivo diffusion imaging named NODDI to capture some of these features in vivo non-invasively. In task 2, we will translate to patients at the early stage of the disease called "clinically isolated syndrome". We will investigate whether the NODDI method validated before or other cutting edge in vivo imaging methods can capture early GM alterations in "key locations" that could be the main substrate for the two important cognitive deficits associated with early MS namely, deficit in episodic memory and slowness of information proces-

Research achievements

sing speed. In task 3, we will use blood samples from patients recruited before (task 2) to phenotype particular T lymphocytes called circulating T follicular helpers (cTfh) that are potentially involved in a primary meningeal inflammation responsible for GM alteration by release of pro-inflammatory factors. We will test the relationship between these potential determinants of meningeal inflammation (alterations in cTfh) and the GM alterations assessed with MRI.

Overall, this project will shade light on multiple determinants of GM alteration associated with MS from the role of meningeal inflammation, to the contribution of activated glial cells, up to the ability to image these features in patients. We expect it could help to understand the substrate of cognitive impairment that is encountered from the early stage of the disease which ultimately could help to develop new therapeutic strategies.

Publications quoting TRAIL:

- Selective dentate gyrus disruption causes memory impairment at the early stage of experimental multiple sclerosis. V. Planche, A. Panatier, B. Hiba, E. Ducourneau, G. Raffard, N. Dubourdieu, M. Maitre, T. Lesté-Lasserre, B. Brochet, V. Dousset, A. Desmedt, S.H. Oliet, T. Tourdias. Brain Behavior and Immunity, dec 2016;
- In Vivo 7T MR Quantitative Susceptibility Mapping Reveals Opposite Susceptibility Contrast between Cortical and White Matter Lesions in Multiple Sclerosis. X W. Bian, X E. Tranvinh, X T. Tourdias, X M. Han, X T. Liu, X Y. Wang, X B. Rutt, and X M.M. Zeineh, AJNR, oct 2016.

IBIONI

Imaging Biomarkers of experimental and clinical neuroinflammation

- Oncology
- Bruno Brochet, the "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2012
- TRAIL funding: 310 654 €

This translational scientific project associates different neuroimaging, neuroepidemiological and neuroscience teams to study mechanisms and consequences of neuroinflammation using new imaging biomarkers in experimental models and human diseases, such as multiple sclerosis (MS). We will study (1) lateral diffusion along the astrocyte membrane of AQP4 in live cells using quantum dot imaging; (2) Validation of new biomarkers for tissue integrity characterisation in experimental models of MS using new high-sensitivity Diffusion Tenser Imaging (DTI), MR Diffusion kurtosis Imaging (DKI) and Diffusion Spectrum Imaging (DSI); (3) application of DTI, fMRI and Voxel based morphometry (VBM) to study the mechanisms of cognitive impairment in MS; (4) application of MRI markers in large cohorts of MS patients (OFSEP) and controls (I-Share).

Publications quoting TRAIL:

- Stroke location is an independent predictor of cognitive outcome, F. Munsch*; S. Sagnier MD*; J. Asselineau PhD; A. Bigourdan MD; C.R. Guttmann MD; S. Debruxelles MD; M. Poli MD; P. Renou MD; P. Perez MD PhD; V. Dousset MD PhD; I Sibon MD PhD*; Thomas Tourdias MD PhD*. Stroke, nov 2015;
- Early Fiber Number Ratio Is a Surrogate of Corticospinal Tract Integrity and Predicts Motor Recovery After Stroke, Antoine Bigourdan, MD*; Fanny Munsch, PhD*; Pierrick Coupé, PhD; Charles R.G. Guttmann, MD; Sharmila Sagnier, MD; Pauline Renou, MD; Sabrina Debruxelles, MD; Mathilde Poli, MD; Vincent Dousset, MD, PhD; Igor Sibon, MD, PhD; Thomas Tourdias, MD, PhD, Stroke, March 2016;
- Cervical spinal cord DTI is improved by reduced-FOV with specific balance between numbers of diffusion gradient directions and numbers of averages; A Crombé, N Alberti, B Hiba, V Dousset, T Tourdias, AJNR, May 2016;
- Information processing speed impairment and cerebellar dysfunction in relapsing-remitting multiple sclerosis. . Ruet A, Hamel D, Deloire MS, Charré-Morin J, Saubusse A, Brochet B. J Neurol Sci. 2014 Oct 12;347(1-2):246-250;
- Hippocampal microstructural damage and memory impairment in clinically isolated syndrome, Planche V at al., MS journal., oct 2016.

INNES

Investigation on Neuronal Energetic Substrate

■ Neurology	■ Anne-Karine Bouzier-Sore, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
■ 2011	■ TRAIL funding: 300 579 €

Glucose is considered as the main brain energy substrate. However, increasing evidence now suggest that lactate, coming from astrocytes, could be a supplementary and very efficiency energetic fuel for neurons, especially during brain activation as well as during hypoxia. The aim of this project will be to characterize the role of lactate as a substrate for neurons during brain activation. Both ex vivo and in vivo situations will be studied. Originality of the ex vivo experiments is to directly analyze metabolism on brain biopsies using Nuclear Magnetic Resonance (NMR) at High Resolution at the Magic Angle Spinning (HR-MAS) spectroscopy after perfusion of 13C-labeled substrates in awake rats. Resting as well as activated conditions (unilateral stimulation of the whisker-to-barrel pathway) will be compared. To model brain metabolism, 13C-labeled glucose and lactate will be infused to animals during 1h, to reach the isotopic steady state. To determine whether MCT2 (neuronal monocarboxylate transporter) is involved in the transfer of astrocytic lactate to neurons, the same experimental procedure will be performed in rats in which MCT2 will be silenced using lentiviral approach. In vivo experiments will be also designed to follow in real-time brain lactate by localized NMR spectroscopy and molecular imaging of lactate at 7T also during whisker stimulation. Finally, we will investigate the implication of such a lactate shuttle between astrocytes and neurons and will perform experiments on neonate model of brain hypoxia to study whether lactate administration directly after hypoxia could be neuroprotective and therefore used as a therapeutic tool.

Publications quoting TRAIL:

- High-resolution NMR-based metabolic detection of microgram biopsies using a 1-mm HRµMAS prototype probe. Analyst, accepted 2015, Yusuke Nishiyama, Yuki Endo, Takahiro Nemoto, Anne-Karine Bouzier-Sore and Alan Wong;
- Rapid adaptation of rat brain and liver metabolism to a ketogenic diet: an integrated study using 1H- and 13C-NMR spectroscopy. Maggie Roy, Marie-Christine Beauvieux,Jérôme Naulin, Dounia El Hamrani, Jean-Louis Gallis, Stephen C Cunnane and Anne-Karine Bouzier-Sore, Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism, Mars 2015;
- Uncertainties in pentose-phosphate pathway flux assessment underestimate its contribution to neuronal glucose consumption: relevance for neurodegeneration and aging, Anne-Karine Bouzier-Sore and Juan P. Bolaños, Front Aging Neurosci. 2015; 7: 89;
- Evaluation of a high-resolution micro-sized magic angle spinning (HRmMAS) probe for NMR-based metabolomic studies of nanoliter samples, Nghia Tuan Duong, Yuki Endo, Takahiro Nemoto, Hiroshi Kato, Anne-Karine Bouzier-Sore, Yusuke Nishiyamaab and Alan Wong, Analytical Method, Aug 2016;
- 13C-NMR spectroscopy applications to brain energy metabolism, Tiago B. Rodrigues, Julien Valette and Anne-Karine Bouzier-Sore. Frontiers in Neuroenergetics, déc 2013;
- Glucose and lactate metabolism in the awake and stimulated rat: a (13)C-NMR study. Sampol, D., Ostrofet, E., Jobin, M. L., Raffard, G., Sanchez, S., Bouchaud, V., Franconi, J. M., Bonvento, G., and Bouzier-Sore, A. K. Front Neuroenergetics 5, 5 (2013).

Research achievements

IPALICA

Inflammatory pathways leading to intracranial aneurysm growth

■ Neurology	■ Jérome Berge, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
■ 2015	■ TRAIL funding: 35 000 €

Intracranial aneurysm (IA) rupture with subsequent subarachnoid haemorrhage remains a life-threatening medical emergency despite recent diagnostic and therapeutic advances. Through a multidisciplinary approach this project aims at characterizing inflammatory and metabolic profiles in patients with ruptured or non ruptured IAs. The aneurysmal sac will be harvested and analyzed through transcriptomic, metabolomic and histologic approaches. Finally, we will characterize in vitro the trigger and the inflammasome pathway responsible for IL1 secretion in patients with ruptured IAs because we foresee that inflammasome-mediated IL-1β secretion observed in aneurismal sac is directly triggered by metabolites that accumulate due to metabolic dysfunction. Collectively these different techniques will allow us to investigate numerous pathways of inflammatory processes in the aneurismal wall in a steady state before rupture and after subarachnoid hemorrhage. Ultimately our goal is to bring new therapeutic targets in patients with IAs.

SCICOG&REACTIV

Bio-imaging markers of tissue integrity, predictors of cognitive impairment in inflammatory demyelinating diseases

■ Neurology	■ Bruno Brochet, the "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
■ 2011	■ TRAIL funding: 130 000 €

Multiple Sclerosis (MS) is the main non-traumatic cause of neurological disability in young adults. There is growing evidence that the clinical disability in MS is not only due to motor deficiencies but also to cognitive deficiencies. Cognitive deficiencies could occur at the early stages of MS (high-risk clinicallyisolated syndromes (CIS) and early MS) and concern mainly information processing speed (IPS) and memory. Recent works suggested that cognitive deficiencies correlate with MRI parameters reflecting diffuse alteration in brain white matter leading to disconnection between cortical areas but also with atrophy of the brain gray matter. The aim of this project is to determine which MRI parameters could be use as a biomarker to predict cognitive deficiencies in CIS and which MRI parameters could predict the responsiveness of MS patients to cognitive rehabilitation. Two parameters will be studied, fractional anisotropy in brain normal-appearing white matter using diffusion-tensor-imaging and volumetric change in brain gray matter using Voxel-Based Morphometry. This project is based on two clinical studies, the SCI-COG, a one-year longitudinal study of CIS patients starting early 2012 and the REACTIV study, an on-going controlled trial of cognitive rehabilitation in MS. This is a 36 months project. Both studies received funding from industrial partners and ARSEP but this application concerns the need for additional human resource (study engineer) to complete image analysis

Publications quoting TRAIL:

- Cerebellar assessment in early MS, Moroso A et al., Cerebellum journal, oct 2016;
- Posterior lobules of the cerebellum and information processing speed at various stages of multiple sclerosis, Moroso A et al., JNNP journal, oct 2016;
- Cognitive evaluation by tasks in a virtual reality environment in multiple sclerosis; D Lamargue-Hamel D, Deloire M, Saubusse A, Ruet A, Taillard J, Philip P, Brochet B. Paper in press in J Neurol Sci;
- Deciphering depressive mood in relapsing-remitting and progressive multiple sclerosis and its consequences on quality of life. Delphine Lamargue Hamel, Mathilde Deloire, Aurélie Ruet, Julie Charré-Morin, Aurore Saubusse, Jean-Christophe Ouallet, Bruno Brochet. Paper in press in PLOS ONE.

TBI

Longterm neurovascular unit changes after mild traumatic brain injury: potential biomarker & Vasc-TBI

■ Neurology	■ Jérome Badaut, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
■ 2015	■ TRAIL funding: 150 000 €

Mild traumatic brain injury (mTBI) is known to induce long-term brain disorders with increased risk of neurodegenerative diseases and reductions in patient lifespan. As mTBI is characterized by undetectable or only minor anatomical changes using traditional neuroimaging techniques, its diagnosis relies mostly on verbal reports of the patient. For these reasons, it is difficult to follow injured patients over time and to deliver appropriate treatments. Our previous research supports the following working hypothesis: TBI induces long-term phenotypic changes of the neurovascular unit (NVU) associated with the emergence of cognitive dysfunction. We will examine this hypothesis in a unique translational project spanning from ex-vivo evaluation in rodent models to clinical monitoring of mTBI patients seeking care at the University of Bordeaux Hospital (CHU Bordeaux).

The present study will offer an extraordinary opportunity to study the potentially protective effects of JNK inhibition in mTBI through a systematic examination of the molecular mechanisms regulating eNOS and the role of such activations on cerebrovascular dysfunction after mTBI, with a focus on the endothelial and smooth muscle layers. This mechanistic study would establish the basic rationale for the importance of following cerebral perfusion as a new biomarker in parallel to the behavioral evaluation. The project will be testing: 1- ex vivo cellular mechanisms of cerebral damages after mTBI; 2-new imaging modalities in mTBI animal models to identify anatomical substratum of behavior dysfunction; 3-new multi-modal neuroimaging protocols to assess the structural and physiological changes over the time in correlation with the behavioral outcomes.

As many mechanisms of pathophysiology are shared among TBI, stroke, subarachnoid hemorrhage, and intra-cerebral hemorrhage, the proposed studies will also offer unique insights into the potential roles of JNK in cerebral responses to these injuries as well as their translation to the clinic setting.

Publications quoting TRAIL:

- Improved long-term outcome after transient cerebral ischemia in aquaporin-4 knockout mice, Lorenz Hirt*, Andrew M Fukuda*, Kamalakar Ambadipudi,-Faisil Rashid, Devin Binder, Alan Verkman, Stephen Ashwal,Andre Obenaus and Jerome Badaut, JCBFM, janvier 2016;
- Chronic cerebrovascular dysfunction after traumatic brain injury. Jullienne A, Obenaus A, Ichkova A, Savona-Baron C, Pearce WJ, Badaut J. J Neurosci Res. Jul 2016.

Research achievements

TRANSFEAR

Translational study of the cerebral substrates involved in pathological fear recovery

- Neurology
- Melissa Bonnet, the "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2012
- TRAIL funding: 130 000 €

Anxiety Disorders including post-traumatic stress disorders (PTSD) are the most common mental disorders with an estimated lifetime prevalence of 15% -20% in the general population. They occur early in life and are risk factors for other mental disorders later in life such as affective disorders and substance abuse disorders thus presenting a major health problem in industrialized countries (WHO and WONCA 2008). In recent years, it has become evident that associative learning mechanisms and alteration in sleep architecture play a crucial role in relapse of fear behaviors. Indeed, it is known that exposure to stimuli that have been repeatedly associated with traumatic events can precipitate fear behavior during relapse and that the lack of extinction consolidation during post-extinction sleep correlates with high fear recovery. While tremendous progress has been made in identifying the basic mechanisms underlying acquisition of fear and consolidation of extinction, much less is known about the neuronal mechanisms involved in fear relapse after extinction. The present translational proposal aims at identifying the changes in functional connectivity of cerebral structures involved in relapse of fear behavior using innovative technologies in both animal and humans. Firstly, we will develop and validate a fear conditioning and extinction protocol in healthy humans, which shares similarities with that currently used in rodents, in order to provide a strong physiological background on fear extinction mechanisms in healthy context. Secondly, we will study the changes in functional interactions between neuronal structures involved in fear and extinction learning during fear behavior using electrophysiological recordings in rodents and functional Magnetic Resonance Imaging (fMRI) technique in humans. Finally we will assess sleep modifications in rodents and healthy humans by using neuronal recordings and electroencephalography (EEG), respectively. The proposed studies will reveal how the functional organization of specific neural structures directly modulates relapse of fear behavior using relevant animal and human models. Elucidating the neural mechanisms mediating pathological fear recovery should further suggest novel therapeutic strategies for psychiatric conditions characterized by a high propensity to relapse such as PTSD.

Publications quoting TRAIL:

- 4-Hz oscillations synchronize prefrontal–amygdala circuits during fear behavior, Nikolaos Karalis, Cyril Dejean, Fabrice Chaudun, Suzana Khoder, Robert R Rozeske, Hélène Wurtz, Sophie Bagur, Karim Benchenane, Anton Sirota, Julien Courtin & Cyril Herry, Nature Neurosciences, Feb 2016;
- Preventing long-lasting fear recovery using bilateral alternating sensory stimulation: a translational study, Wurtz, El-Khoury-Malhame, Wilhelm, Michael, Beetz, Roques, Reynaud, Courtin, Khalfa, Herry, Neuroscience, May 2016;
- Neuronal Circuits for Fear Expression and Recovery: Recent Advances and Potential Therapeutic Strategies. C. Dejean, J. Courtin, R. Rozeske, M. C. Bonnet, V. Dousset, T. Michelet, and C. Herry. Biological Psychiatry Sep, 2015; 78:298–306.

BIOPSYPROSTAPROBE

Antibody-based fluorescence probe for biopsy guidance of prostate cancer

- Oncology
- Franck Couillaud, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2014
- TRAIL funding: 35 000 €

Prostatic carcinoma is the most common cancer affecting one in six and is a leading cause of cancer mortality. Cancer detection include imaging and tumor biomarker dosage like PSA (prostate-specific antigen), but actually all of examinations cannot diagnose prostate cancer at an early stage with sufficient confidence. Therefore a tumor biopsy is required to confirm the presence of the tumor, its size and its grade. Because these biopsies are negative in around 60% of cases, new methods for biopsy guidance are required. As member of the The BiTum consortium, we have proposed to combine

fluorescence imaging to the ultrasound imaging currently used in clinic, in order to detect small prostate tumors making possible to guide the transrectal biopsy . The goal of the current project is to develop a fluorescescent probe based on a labeled antibody. We have selected a ScFv fragment of the monoclonal D2B anti-PSMA antibody, provided by our Italians collaborators to be labeled with a near infrared fluorophore. This fragment is known to specifically targeted in vivo subcutaneous tumor in mice. The test probe efficiency in physiopathological context as close as possible of clinical conditions, we are proposing to develop a prostate cancer model using mouse RM1 cells in immunocompetent mice. RM1 cells will be genetically modified to express both human PSMA and imaging reporter genes in order to test labeling specificity. Completion of the current project will open avenue for translational application of ScFv fragment for biopsy guidance of prostate cancer. That's why this innovative way of the project has appeared in directly coupling the scFvD2B fragment to a near infrared fluorophore

Publications quoting TRAIL:

- In vivo imaging of prostate cancer using an anti-PSMA scFv fragment as a probe, Mazzocco C, Fracasso G, Germain-Genevois C, Dugot-Senant N, Figini M, Colombatti M, Grenier N & Couillaud F, Scientific Reports 6, 23314, Mar 2016.

MIMATHUMAB

Molecular IMaging of ATHeroma with HUMan AntiBody

■ Cardiology	■ Gisèle Clofent-Sanchez, the Centre of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
■ 2012	■ TRAIL funding: 295 000 €

MIMATHUMAB project focuses on molecular imaging of atherosclerosis, using human antibody discovery for high quality functionalization of nanoparticles dedicated to safe and non-invasive magnetic resonance imaging (MRI) and for radiolabeling with 18F for positron emission tomography (PET). This translational project at the crossroads of WP5 and cardiology domain is part of a wider interdisciplinary research aimed at developing a theranostic approach for atherosclerosis. Atherosclerotic lesions (atheroma), the leading cause of the majority of cardiovascular disorders, are asymmetric focal thickenings of the innermost layer of the artery, the intima. They consist of cells, connective-tissue elements, lipids and debris. Atherosclerosis is a disease involving endothelial dysfunction, oxidative stress, immunity, inflammation and calcification. The inflammatory lesions evolve to vulnerable plaques at high risk of rupture and thrombi formation, thus precipitating the clinical conditions of stroke and myocardial infarction, the main causes of death in the Western world. The goals for the years to come must include translation of the experimental work to the visualization of appealing biologic targets in humans. Nowadays, there is an increasing interest in molecular imaging of atherosclerosis, in order to assess the cellular components that underlie the risk of rupture. Molecular imaging requires highly sensitive and specific probes made of a signal detection compound and an affinity ligand for targeting. In this project, we aimed to achieve molecular imaging by functionalizing imaging devices with recombinant human single chain Fv (scFv) antibodies (Abs) designed to target vulnerable plaques developed in atherosclerosis. MIMATHUMAB differs from international competition as it offers human antibodies (Abs) targeting relevant biomarkers to functionalize multimodal nanoparticles. Our team has the know-how for in vivo selection of human Abs in animal models of atherosclerosis. This emerging project is initiated with an international team also deeply involved in atherosclerosis and antibody research for use in human beings. In order to implement a new strategy to diagnose atherosclerosis by MRI, we also need strong contrast agents. We therefore come closer to UPR9048 CNRS (Institut de Chimie de la Matière Condensée de Bordeaux, groupe 5 « Chimie des nanomatériaux ») which has recently developed a platform of superparamagnetic nanoparticles, the VUSPIO (Versatile Ultrasmall SuperParamagnetic Iron Oxide) platform that can accommodate targeting ligands such as chimeric or fusion proteins, peptides or antibodies. The project offers the unique opportunity to develop recombinant strategies and agents starting from the initial design up to the final in vivo evaluation. Owing to its multidisciplinary competences, this project takes on special importance within TRAIL, which leans by definition on translational and multidisciplinary approaches.

Research achievements

Publications quoting TRAIL:

- Nanoparticles functionalised with an anti-platelet human antibody for in vivo detection of atherosclerotic plaque by Magnetic Resonance Imaging. M.J Jacobin-Valat, J. Laroche-Traineau, M. Larivière, S. Mornet, S. Sanchez, M. Biran, C. Lebaron, J. Boudon, S. Lacomme, M. Cérutti, G. Clofent-Sanchez. Nanomedicine: Nanotechnology, Biology, and Medicine, 2014;
- Solid Lipid Nanoparticles for Image-Guided Therapy of Atherosclerosis, Khalid Oumzil, Michael A. Ramin, Cyril Lorenzato, Audrey Hémadou, Jeanny Laroche, Marie Josée Jacobin-Valat, Stephane Mornet, Claude-Eric Roy, Tina Kauss, Karen Gaudin, Gisèle Clofent-Sanchez, and Philippe Barthélémy, Bioconjugate Chemistry, jan 2016;
- A Recombinant Human Anti–platelet scFv Antibody Produced in Pichia pastoris for Atheroma Targeting. Amelie Vallet–Courbin, Mélusine Larivière, Agnès Hocquellet, Audrey Hemadou, Sarjapura–Nagaraja Parimala, Jeanny Laroche–Traineau, Xavier Santarelli, Gisèle Clofent–Sanchez, Marie–Josée Jacobin–Valat and Abdelmajid Noubhani. PLoS ONE, dec 2016.

STEAMRI

Whole lung oxygen-enhanced imaging in humains using MRI

■ Pneumology	■ Gael Dournes, the Bordeaux Cardio-Thoracic Research Centre (CRCTB, U1045)
■ 2016	■ TRAIL funding: 40 000 €

The aim of the project is to assess the feasibility to perform whole lung oxygen-enhanced (OE) imaging in humans using MRI with the PETRA sequence.

■ B.16 Work package "mathematic simulation and modeling"

ARM

Automatic assessment of Radiofrequency ablation Margins

■ Oncology	■ Baudoin Denis De Senneville, the Bordeaux Institute of Mathematics (IMB, UMR5251)
■ 2016	■ TRAIL funding: 150 000 €

Hepatocellular carcinoma (HCC) is the most frequent liver cancer (a primitive cancer of the liver) and more than 90% of HCC occurs on liver cirrhosis in western country. Percutaneous thermo-ablation, especially radiofrequency performed under CT-Scan guidance, has become the first-line treatment for hepatocellular carcinoma. Prognosis after radiofrequency ablation (RFA) is impaired by the risk of local tumor recurrence but also by de-novo HCC developed from liver cirrhosis. The main cause of local tumor recurrence is an insufficient ablative margin around the tumor (at least 5mm recommended, ideally 1-2cm). Untreated microscopic satellite nodules due to insufficient margin leads to local tumor recurrence. Unfortunately, at odd with surgical resection where pathological analysis of the tissue resected provides the safety margin around the tumor, the technical success of percutaneous thermo-ablation is assessed only by CT-scan or MR examination. The development of an automatic assessment of treatment margin will offer great perspective improving efficacy of radiofrequency ablation.

The aim of this project is to propose a fully automatic pipeline to a fast assessment of 3D-treatment margins that could allow performing additional heating cycle in order to achieve a complete treatment with satisfying margins. The methodology will be the following one: we will develop (implement?) an elastic registration between the post and pre-RFA imaging. We will develop a post-processing technique designed to 3D-treatment margins either on CT-scan or MRI. Furthermore this pipeline will also use to predict local tumor recurrence according to 3D-treatment margins. So computing safety margin after thermoablation required imaging registration between the Pre and Post-treatment scan, a segmentation of the tumor and the ablative area and computing the safety margin.

Axis 1: Calculation and assessment of the RF 3D-margin to improve RF accuracy during the procedure

The first axis of our study aims at using the proposed post-processing technique for the assessment of the treatment success during the thermoablation in order to improve the efficacy of treatment. The objective is to avoid local tumor recurrence by achieving 1 or 2cm safety margins all around the tumor (in 3D), based a fast and semi-automatic 3D-margin computation, during an RFA procedure (under MRI, cone-beam CT, or CT-Scan guidance). Hence RF-technique probes could be moved to insufficient treated areas in order to complete the ablation during the same session. This should drastically reduce local tumor recurrence arising from insufficient margins and multiple RF-sessions to treat the same nodule. The post-processing technique will include a fully automatic registration of the pre- and post-RFA images, a semi-automatic segmentation of the pre-RFA tumor and the post-RFA ablation volume, and a subsequent calculation of the 3D margins. However, it can be anticipated that the techniques will be time consuming and so misfit to clinical practice. Thus, we intend to accelerate the developed algorithms in order to achieve a fully automatized technique taking fewer than 10 minutes for full process.

Axis 2: Calculation and assessment of the RF 3D-margin to improve follow-up and prognosis

The aim of Axis 2 is to use the full post-processing technique developed in Axis 1 to measure the tumor surface area with insufficient ablative margin (<5mm) and to assess its potential to predict local tumor progression two years post RFA. The post-processing technique will include a fully automatic registration of the pre- and post-RFA images, a semi-automatic segmentation of the pre-RFA tumor and the post-RFA ablation volume, and a subsequent calculation of the 3D exposed tumor surface area. The ability to use TAEIM surface to predict local recurrence at 2 years will be tested on cirrhotic patients treated by RFA.

Combining all these ideas could provide a great toolbox to assess the prognosis of cirrhotic patients treated for HCC by RFA and improving their managements; i.e. earlier liver transplantation, shorter time between two MR imaging follow-up. Within this project, we also plan to evaluate the potential of the developed post-processing techniques for the estimation of the recurrence of lung metastases using CT-Scans.

MOD

Mathematical modeling of the response to antiangiogenic drugs via medical imaging

- Oncology
- 2013
- Thierry Colin, the Bordeaux Institute of Mathematics (IMB, UMR5251)
- TRAIL funding: 380 000 €

The aim of this project is to propose mathematical models for evaluating the response to anti-angiogenic drugs using functional imaging. The ultimate goal of this approach will be to be able to propose numerical tools in order to predict the evolution of the growth of a tumor or its long-term response to a treatment using the early response, measured through functional imaging.

The methodology will be the following one: we start by writing a mathematical model (using a set of partial differential equations) that relies on a mechanistical description of the tumor growth. Usually, this model will involve a set of "free" parameters (less than 10) that are unknown and to be determined. Then we check that this model is able to describe, at least qualitatively, the behaviors that are observed on longitudinal series of CT-scans or MRI. At this point two strategies are available: 1/ The first one consists in trying to describe the characteristics of the image (as for example the texture of the image of the tumor) through the model in order to explain the effect of the drugs. For example, it is well known that the effect of anti-angiogenic drugs may not only be observed on the change of shape of the tumor but also on its constitution. Using series of longitudinal data, we will try to highlight new numerical markers evaluating the long-term response to the therapy. 2/ The second approach will be to provide patient-specific prognosis: we try to find the «best» values of the parameters that allow to match with the series of imaged by solving an optimization problem; then me make a prediction using this set of parameters. This strategy has been successfully used for evaluating the aggressiveness of lung metastases without treatment in the team MC2 of T. Colin. We will develop this methodology in two directions. The first axis is devoted to NSCLC and brain metastasis and the second one to kidney cancers and lung metastasis. We will develop below the specificity in terms of imaging of both axes.

Axis 1: Modeling the response of NSCLC to Avastin

We plan to use diffusion MRIs in order to parametrize the model as well as the new sequences developed in the team of S. Miraux. This study will rely on a clinical trial in Ber-

gonié (J. Palussière). Experiences on the small animal will be provided by the team of A. Bikfalvi. The modeling part will be done in the team of T. Colin.

The RMSB team led by S. Miraux has the expertise in 3D small animal MR imaging for the detection of small brain metastases in vivo, without requiring the use of any contrast agent. These methods allow for longitudinal studies and tumor volume quantifications in order to get the information necessary to develop a predicting model of tumor growth. However, imaging lungs, in small animals as well as in humans, remains a challenge in MRI due to its really low SNR, respiratory motion and susceptibility artifacts generated by the air-tissue interface.

For this purpose, novel radial MR sequences (Gradient echo or trueFISP) will be performed and optimized in order to obtain high contrast between metastases and healthy lungs without any artifacts on the MR images.

This optimization will be performed on a 7T pre-clinical scanner for small animal (RMSB) and in parallel on a 1.5T clinical scanner at Bergonié Institute (in collaboration with Siemens).

For the pre-clinical study, a well-known model of brain metastasis using human breast cancer cells will be used to validate the optimization of the MR sequences. These data will have to be accurate enough for computer scientists to establish a mathematical model predicting the metastases growth in the mouse brain.

In a second step, to get closer to the clinical practice, renal tumor cells will be orthotopically injected into mice inducing pulmonary metastasis (INSERM U 1029). The MR sequence optimization followed by the mathematical model will be tested and compared with brain metastases.

For clinical studies, patients developing pulmonary metastasis will be selected and longitudinally imaged using the optimized sequences (Bergonié).

Axis 2: Modeling the response of renal cell carcinomas (RCC) to anti-angiogenic drugs

The strategy will be similar to axis one and concerns RCC with or without metastases to other organs (pancreas, lung). Based on the key step of hypoxia, which promotes cancer development, we will integrate parameters obtained from several imaging techniques in order to improve the accuracy of the model.

The first step will be to obtain test data from specific MR sequences, such as Dynamic Contrast Enhanced or BOLD sequences, provided by the 3T clinical MRI of Pellegrin Hospital (F. Cornelis, N. Grenier) with the technical support of General Electrics (B. Perez). All these imaging techniques are currently developed and added to the morphologic MR evaluation performed during clinical studies on RCC directed by A. Ravaud (St André Hospital).

New algorithms of real time adaptive distortion correction (B De Senneville) will be progressively integrated in these MR acquisitions. The second step will be to integrate data obtained from specific radioactive markers for TEP scan (P. Fernandez, H. de Clermont) focus on hypoxia such as F miso.

Publications quoting TRAIL:

- Patient-specific simulation of tumor growth, response to the treatment, and relapse of a lung metastasis: a clinical case. Thierry Colin, François Cornelis, Julien Jouganous, Jean Palussière and Olivier Saut, Jouganous et al. Journal of Computational Surgery (2015) 2:1;
- Computational Trials: Unraveling Motility Phenotypes, Progression Patterns, and Treatment Options for Glioblastoma Multiforme, Fabio Raman, Elizabeth Scribner, Olivier Saut, Cornelia Wenger, Thierry Colin, Hassan M. Fathallah-Shaykh*, PlosOne, jan 2016;
- Lefebvre G., Cornelis F., Cumsille P., Colin T., Poignard C., Saut O. Spatial Modeling of Tumor Drug Resistance : the case of GIST Liver Metastase, to appear in Mathematical Medicine & Biology, March 2016;
- Computational Modelling of Metastasis Development in Renal Cell Carcinoma, Etienne Baratchart, Sébastien Benzekry*, Andreas Bikfalvi*, Thierry Colin*, Lindsay S. Cooley, Raphäel Pineau, Emeline Ribot, Olivier Saut, Wilfried Souleyreau, PlosOne Nov 2015.

NEKOMRI

MRI sequence for bronchial wall segmentation and analysis

- Pneumology
- Fabien Baldacci, the Bordeaux Cardio-Thoracic Research Centre (CRCTB, U1045)
- 2014
- TRAIL funding: 35 000 €

The aim of this project is to develop bronchial wall segmentation and analysis methods on a new MRI sequence for lung acquisition, allowing both a diagnosis by using a MRI instead of CT scan, and the assessment of bronchial remodeling.

HETEROMRMAP

MR mapping of renal function heterogeneity to characterize parenchymal nephropathies

- Nephrology
- Benjamin Taton, the Bordeaux Institute of Mathematics (IMB, UMR5251)
- 2016
- TRAIL funding: 50 000 €

Glomerular filtration rate (GFR) is the hallmark of kidney function. The current estimation or measurement techniques are either questionable or constraining and provide only a global estimation of the GFR for both kidneys.

Dynamic contrast-enhanced MRI (DCE-MRI) is a promising tool to build functional maps of the kidneys. A bolus of gadolinium-based contrast media (GCM) is infused in the patient's bloodstream and images of the investigated kidney and a feeding artery are iteratively acquired over a few minutes. A mathematical model describes the distribution of the GCM in the kidney. Fitting this model with the acquired data yields estimations of the GFR and of other relevant parameters (perfusion, tubular transit time...) on a voxel-by-voxel basis. Currently these techniques lack precision, which prevents them from being used as a routine examination to measure global GFR. In contrast, they exhibit a good intra-individual reproducibility and functional maps are probably a reliable estimation of the relative filtration capability of the different zones of the kidney cortex.

As for other organs, and based on previous studies, we assume that the heterogeneity of the functional parameters in the kidney may characterize the underlying parenchymal diseases and their prognosis, a hypothesis that has never been checked before, but seems plausible in the basis of the focal nature of many renal diseases within the kidneys, whether glomerular of interstitial. DCE-MRI could be a non-invasive adequate tool to build the functional maps required to assess this assumption.

This project would be a pilot study to investigate the spatial variability of the functional parameters in the kidney in controls and in patients with well-characterized diseases (diabetic nephropathy, glomerulonephritis mediated by inflammatory processes).

B.17 Work package "cohort imaging methodology"

ABACI

Automated Brain Anatomy for Cohort Imaging

- Neurology
- Bernard Mazoyer, the Neurofunctional Imaging Group (GIN, UMR5296)
- 2012
- TRAIL funding: 314 830 €

The ABACI project (Automated Brain Anatomy for Cohort Imaging) consists in developing, testing and applying a software toolbox dedicated to the automated processing of structural MRI, acquired in the framework of cohort studies. The project closely fits with the TRAIL laboratory of excellence strategic plan that includes population neuroimaging as one of its key topic. The project federates three neuroimaging teams of TRAIL with two non-TRAIL teams specialized in neuroepidemiology. Unsupervised pipelines for registration, normalization, segmentation and morphometric analysis of structural brain MRI acquired in large longitudinal cohorts will be implemented. These pipelines will deliver global and regional brain anatomy phenotypes for grey matter, white matter and CSF. Whenever possible, widely used and validated public domain neuroimage processing algorithms will be integrated. The project will be linked to and run in parallel with i-Share, a large size MRI cohort of students that will serve as a test cohort for the toolbox. In addition, all participating teams will have the opportunity to test and adapt the tools to their own cohorts and settings, with opening applications in the fields of multiple sclerosis, stroke and brain aging. Commercial use of the toolbox by non-academic users will be proposed.

Research achievements

ACTE

Ambulatory cognitive training in elderly: Relation with intrinsic brain functional connectivity

- Neurology
- Sandra Chanraud, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2012
- TRAIL funding: 130 000 €

Age-related cognitive decline has multiple brain substrates including compromised integrity of cortical gray matter nodes, white matter connections, and cerebrovascular perfusion. Successful aging involves functional neuroadaptation to accommodate to or compensate for these multi-level changes in brain microstructure and macrostructure and the potential to enhance function with redistribution of resources. Cognitive training from computerized tools holds promise for improving cognitive abilities in cognitively normal, community-dwelling older adults who have a higher risk of cognitive decline, due to a low "cognitive reserve" as they age. Even though benefits on psychological measures of training in elderly have been well documented, little is known on neural substrates underlying this cognitive gain. It is known, however, that frontostriatocerebellar networks underlie changes from controlled to automatic behaviors involved in learning processes launched during task training. Also, functional connectivity of the "default-mode" network (DMN), which is specific to the resting brain, has been revealed to predict task performance after training. Therefore, we propose to identify, in elderly neurophysiological substrates of training-induced plasticity using resting-state connectivity, and functional activation measures together with measures of cognitive efficiency induced via tasks training, using ambulatory and computerized techniques. These studies will be directed by three overarching hypotheses: 1) training processes will help subjects to establish automatic processes through changes of resting functional connectivity 2) the extent of training-related changes from controlled to automatic processes will be related to functional connectivity changes within and between specific neural networks, i.e., frontostriatocerebellar and defaultmode networks 3) greater anticorrelation between task- and rest- networks will correlate with greater local functional connectivity and better performance.

Publications quoting TRAIL:

- Neuroimaging and Alcoholism. Chanraud S, Bernard C. Annales Médico-Psychologiques 2015;
- Compensatory recruitment of neural resources in chronic alcoholism. Chanraud S. and Sullivan EV. Handbook of Clinical Neurology, Vol. 125, 2014.

ADPP

Brain Topology of AD presymptomatic phase

- Neurology
- Gwenaelle Catheline, the Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2015
- TRAIL funding: 30 000 €

It is now admitted that AD is a long run disease, with a long presymptomatic phase. The application of disease-modifying therapy at this very late phase of the disease could partly explain its inefficiency. That is why studies on AD are now focusing on the presymptomatic phase of the disease. Retrospective studies with follow-up covering decades are the only way to study the real presymptomatic phase by describing AD incident cases. Based on these studies, AD subjects present cognitive impairment several years before clinical diagnosis. Moreover, retrospective neuroimaging studies on AD converters subjects highlight the presence of morphological modifications occurring at the level of temporo-parietal regions at least 5-7 years before diagnosis. Whereas, morphological data are now available several years before AD diagnosis, for more recent MRI methodology such as rest fMRI and DTI data no such hindsight are available. However, recent studies indicate that modifications of functional and structural networks are present on cognitively normal subjects at risk for AD. Finally, the link between modifications of the connectome and the emergence of cognitive symptoms is not yet fully understood.

Our project will consider structural (through morphological MRI and diffusion MRI) and functional (through rest fMRI) networks modifications underlying cognitive decline in elderly subjects. Moreover, most previous studies described

separately structural and functional networks, whereas no one could ignore the constraint of one on the other. A recent framework based on graph theory could facilitate the exploration of the interaction between structural and functional modifications. We will use here this methodology to first describe separately structural and functional modifications of the topological connectome and to finally integrate these different modalities in one statistical framework. This project is based on two large cohorts of elderly subjects (3City and AMImage studies) with 6 to 10 years follow-up. Based on this multiple time point cognitive assessment, episodic memory and executive function decline will be evaluated for each subject allowing excluding false impaired subjects frequently included in cross-sectional analysis. The results of this project should give some information on the link between cerebral modifications and the emergence of cognitive symptoms in aging subjects, which characterize the presymptomatic phase of AD.

Publications quoting TRAIL:

- Age-Related Modifications of Diffusion Tensor Imaging Parameters and White Matter Hyperintensities as Inter-Dependent Processes, Amandine Pelletier*, Olivier Periot, Bixente Dilharreguy, Bassem Hiba, Martine Bordessoules, Sandra Chanraud, Karine Pérès, Hélène Amieva, Jean-François Dartigues, Michèle Allard and Gwénaëlle Catheline, Frontiers in Aging Neurosciences, jan 2016;
- Activity/rest cycle and disturbances of structural backbone of cerebral networks in aging, Marion Baillet, Bixente Dilharreguy, Karine Pérès, Jean-François Dartigues, Willy Mayo, Gwenaëlle Catheline, Neuroimage, Sept 2016.

TRAIL&TRACKS

Atlasing whole brain white matter tracts in 300 healthy humans

- Neurology
- 2011
- Laurent Petit, the Neurofunctional Imaging Group (GIN, UMR5296)
- TRAIL funding: 97 500 €

The present project proposes, using diffusion tensor imaging (DTI) tractography, to create a normative population-based probabilistic atlas of white matter tracts in healthy humans (TRAIL&TRACKS) for research, clinical and educational purposes. It is based on the BIL&GIN cohort, which includes 300 healthy volunteers aged between 18 and 50 years, balanced between men and women, right-handers and left-handers. The doctoral fellowship application deals with the work to be performed on DTI data, the validation of a method for probabilistic tractography of a set of white matter tracts, the anatomical description of every tracts and how they differ among the 300 subjects in terms of hemispheric asymmetries, gender and handedness. Specific metrics of white matter integrity will be extracted for tracts in the brainstem and projection, association, and commissural tracts. This is not to propose another atlas of the white matter of the human brain, but a tool where inter-hemispheric asymmetry and inter-individual variability will be taken into account into the description of each tract. Once patented, we will deliver an automated tract-labeling tool interfaced with usual neuroimaging analysis software. Several publications are envisaged for the construction of this atlas, including the edition of a textbook and numerical tools such as web-based application for teaching material and training.

Research achievements

COBRASCAN

Quantitative CT and COBRA cohort for study of chronic obstructive pulmonary disease

- Pneumology
- François Laurent, the Bordeaux Cardio-Thoracic Research Centre (CRCTB, U1045)
- 2013
- TRAIL funding: 234 448 €

Chronic obstructive pulmonary disease (COPD) is expected to be the 3rd leading cause of mortality and the 5th cause of morbidity in the world by 2020. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible. Airflow limitation is defined by pulmonary function tests (PFT) results and is caused by narrowing of small airways which is a consequence of the combination of airways wall thickening due to airway wall remodeling and loss of tethering force due to emphysematous lung destruction. However patients with the same airflow limitation will present with different clinical subtypes, in term of severity and outcome. The effect of certain treatments can be only proved in term of primary outcomes if there is a mean other than pulmonary function tests for classifying patients into phenotypes in longitudinal studies. The prognostic impact of these phenotypes is still poorly known.

Advance in CT technology and CT image analysis programs, i.e. CT algorithms herein referred to as quantitative CT (QCT) can be used to analyse in details the morphological changes involved in COPD, i.e. the severity of emphysema, airways dimensions, small airways obstruction and small pulmonary vessels on CT images. Our group has developed software needed for combined quantitative analysis of structural changes of proximal and distal airways and can use software dedicated to quantification of emphysema and pulmonary vessels. However, there is still no consensus in term of the best appropriate algorithms for quantification.

The COBRA project directed by INSERM relies on a national cohort of 500 patients. The main objective of the COBRA cohort is to determine clinical, biological and genetical determinants of the outcome of COPD patients. The recruitment started in 2008 and inclusion of 500 patients is finally expected, 211 of them being included so far. Clinical, functional and biological variables will be followed up over 10 years. COBRASCAN will consist in a QCT acquisition performed in each patient included into the COBRA cohort during the 5th year after inclusion. The hypothesis is that a CT quantitative morphological analysis reflecting lung parenchymal destruction (emphysema), bronchial wall remodeling of large and small airways and changes in pulmonary vessels has a significant prognostic impact. The originality of COBRASCAN will be its ability to identify phenotypes of COPD patients based on multiple morphological criteria and to specify their prognostic value. The innovative aspect of the project is the development of a single new software able to combine the acquisition of objective data of emphysema, bronchial wall thickening of proximal and distal airways, large vessels size, reflecting changes of the whole respiratory system. The software will be built based on the most robust and reproducible algorithms available and the most relevant variables for each type of morphological changes will be determined. The study will specify the role of quantitative CT as a biomarker of COPD, and its position in on-going clinical trials. Phenotyping COPD into appropriate subgroups using imaging in addition to PFT is likely to play a role in pharmacological research.

Publications quoting TRAIL:

- Lung morphology assessment of cystic fibrosis using MRI with ultra-short echo time at submillimeter spatial resolution, Gaël Dournes & Fanny Menut & Julie Macey & Michaël Fayon & Jean-François Chateil & Marjorie Salel & Olivier Corneloup & Michel Montaudon & Patrick Berger & François Laurent, Eur Radiol, feb 2016;
- Quiet Submillimeter MR Imaging of the Lung Is Feasible with a PETRA Sequence at 1.5 T1, Gaël Dournes, MD, PhD, David Grodzki, PhD, Julie Macey, MD, Pierre-Olivier Girodet, MD, PhD, Michaël Fayon, MD, PhD, Jean-François Chateil, MD, PhD, Michel Montaudon, MD, PhD, Patrick Berger, MD, PhD, François Laurent, MD, Radiology, july 2015;
- CT evaluation of small pulmonary vessels area in patients with COPD with severe pulmonary hypertension, Florence Coste, Gaël Dournes, Claire Dromer, Elodie Blanchard, Véronique Freund-Michel, Pierre-Olivier Girodet, Michel Montaudon, Fabien Baldacci, François Picard, Roger Marthan, Patrick Berger, François Laurent, Thorax, april 2016.

B.2 Achievements per work-package, presented by work-packages Coordinators

■B.21 Work package "interventional imaging and MRI guided HIFU" - Coordinator: Bruno Quesson (CRCTB)

Achievements (2011 – 2016): numbers in the text refer to publications in the field listed below

Several research programs have been developed over the last years in the field of MRI guided HIFU, including technological developments, preclinical evaluation and clinical studies. This includes the design of new ultrafast MRI methods to image in real-time (several slices per second) the temperature and acoustic displacement distribution in the heart (3, 4), brain (5), liver (5) and muscle (5). A fully automated imaging pipeline is now available that includes fast acquisition, real-time image reconstruction, and motion correction on mobile organs of the thorax and abdomen with compensation of associated susceptibility artifacts (7). Images are streamed online to a visualization console (Thermoguide™) provided by an industrial partner (Image Guided Therapy SA – Pessac, Dr E Dumont) that also controls HIFU hardware. This allows online feedback to the HIFU generator for optimization of energy deposition at the targeted location for improved safety. Combination of physical modeling of tissue thermal parameters and experimental validation with MR guided HIFU in the liver and kidney should help in optimizing acoustic energy deposition of the therapeutic protocols (16, 17, 18). The use of non-linear propagation of ultrasound at high intensity has been shown to enhance the volume of ablation in the liver while keeping total acoustic energy constant (12, 13).

These new methods have been validated on preclinical models in perspective of clinical transfer (for breast with Anti Cancer Center "Institut bergonié" – Bordeaux (Dr J Palussière), for the brain with Institut langevin and IHU ICM – Paris (Dr JF Aubry), IHU Liryc for cardiac applications (Pr M Haïssaguerre)). Clinical research projects headed by Pr H Trillaud at Hôpital saint-André (Bordeaux) are ongoing for the improvement of the treatment of uterine fibroids (8, 10, 14, 15). Regulatory aspects of the project of treatment of breast cancer are being solved, with the objective to include the first patients in 2017 (international collaboration between Bordeaux university and University of Utah, Pr D Parker). A proof of concept of non-invasive cardiac stimulations with MR guided HIFU has also been published (6) and patented, with short terms perspective of tech transfer toward industry through creation of a local startup company (IHU Liryc).

Other projects are more oriented toward fundamental research and include the use of MR guided HIFU technology for ultrasound mediated local drug delivery in oncology:

1: Development of MRgHIFU tools for in vivo tumor and tumor micro environment non-destructive heating.

This task is currently tested using the Tribop HIFU system (not MRI coupled) using a heat sensitive transgenic mice (11). Thermo-induced gene expression is followed by optical imaging (Fluc) at Vivoptic platform. Experiments will soon move to the 9.4 Tesla MRgHIFU setup at IHU Liryc.

2. Design and synthesis of thermosensitive nano-vehicles.

Preliminary work on the synthesis of thermosensitive nanoparticles (NP) was carried out. Fluorescently labeled silica nanoparticles were chosen as vector (9). As initial step, they have been synthesized and grafted with different densities to PEG macromolecules to study their biodistribution in vivo in mice bearing subcutaneous tumors. The fluorescent NPs in the gaseous state, PEGylated in the saturating state, have interesting physical properties for evaluating the sensitivity of the effect of permeability and improved tumor retention (EPR). Impact of the surface grafting density of PEG macromolecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors (2).

3. In vivo monitoring of HIFU thermo-induced drug delivery.

To study the thermal response, in vivo tumor models based on gene expression of imaging reporter will be used (1). A murine cell line RM1 genetically modified for thermo-induced expression of optical imaging reporter gene in currently in the selection process. This cell line is able to generate subcutaneous, orthotopic tumor in prostate and metastases in Black6 immunocompetent mice and will be used in the thermosensitive mice strain currently in use in task 1.

These developments open new perspectives in image-guided non-invasive therapies in aforementioned organs. WP1 is intrinsically translational, with the objective of developing new concepts in imaging/therapy for better treatment efficiency and enhanced patient safety.

Over the period 2011-2016, acquisition of devices (HIFU devices and MRI scanners) and research team building from scratch was necessary. Close collaboration with industry (imaging and HIFU) has been created, which is a mandatory step to translate these new developments into clinical reality.

Research achievements

Peer reviewed articles, orange stars (*) indicate studies with TRAIL funding

1. (*) Sandre O, Genevois C, Garaio E, Adumeau L, Mornet S and Couillaud F (2017) In vivo imaging of local gene expression induced by magnetic hyperthermia. Genes, in press;
2. (*) Adumeau L., Genevois C., Roudier L., Schatz C, Couillaud F. , Mornet S.(2017) Impact of surface grafting density of PEG macromolecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors. BBA, in press;
3. (*) Toupin S, Bour P, Lepetit-Coiffé M, Ozenne V, Denis de Senneville B, Schneider R, Vaussy A, Chaumeil A, Cochet H, Sacher F, Jaïs P, Quesson B. Feasibility of real-time MR thermal dose mapping for predicting radiofrequency ablation outcome in the myocardium in vivo. J Cardiovasc Magn Reson. 2017 Jan 25;19(1):14;
4. (*) Toupin S, de Senneville BD, Ozenne V, Bour P, Lepetit-Coiffe M, Boissenin M, Jais P, Quesson B. Combination of principal component analysis and optical-flow motion compensation for improved cardiac MR thermometry. Phys Med Biol. 2017 Jan 23;62(4):1208-1224;
5. (*) Bour P, Marquet F, Ozenne V, Toupin S, Dumont E, Aubry JF, Lepetit-Coiffe M, Quesson B. Real-time monitoring of tissue displacement and temperature changes during MR-guided high intensity focused ultrasound. Magn Reson Med. 2017 Jan 16;
6. (*) Marquet F, Bour P, Vaillant F, Amraoui S, Dubois R, Ritter P, Haïssaguerre M, Hocini M, Bernus O, Quesson B. Non-invasive cardiac pacing with image-guided focused ultrasound, Sci Rep. 2016 Nov 9;6:36534;
7. (*) Ozenne V, Toupin S, Bour P, de Senneville BD, Lepetit-Coiffé M, Boissenin M, Benois-Pineau J, Hansen MS, Inati SJ, Govari A, Jaïs P, Quesson B. Improved cardiac magnetic resonance thermometry and dosimetry for monitoring lesion formation during catheter ablation. Magn Reson Med. 2016 Feb 21;
8. Hocquelet A, Denis de Senneville B, Frulio N, Salut C, Bouzgarrou M, Papadopoulos P, Trillaud H. Magnetic resonance texture parameters are associated with ablation efficiency in MR-guided high-intensity focussed ultrasound treatment of uterine fibroids. Int J Hyperthermia. 2016 Oct 28:1-8;
9. (*) Germain-Genevois C, Garandeau O et al. Detection of Brain Tumors and Systemic Metastases Using NanoLuc and Fluc for Dual Reporter Imaging. Mol Imaging Biol, 2016; 18, 62-69;
10. Thiburce AC, Frulio N, Hocquelet A, Maire F, Salut C, Balageas P, Bouzgarrou M, Hocké C, Trillaud H. Magnetic resonance-guided high-intensity focused ultrasound for uterine fibroids: Mid-term outcomes of 36 patients treated with the Sonalleve system. Int J Hyperthermia. 2015;31(7):764-70.;
11. Fortin, PY, Lepetit-Coiffé M, Genevois, C, Debeissat C, Quesson, B, Moonen CT, Konsman JP, Couillaud F. Spatiotemporal control of gene expression in bone-marrow derived cells of the tumor microenvironment induced by MRI guided focused ultrasound. Oncotarget. 2015; 15;6 (27):23417-26;
12. Elbes D, Denost Q, Robert B, Köhler MO, Tanter M, Quesson B. Magnetic Resonance Imaging for the Exploitation of Bubble-Enhanced Heating by High-Intensity Focused Ultrasound: A Feasibility Study in ex Vivo Liver. Ultrasound Med Biol. 2014; 40(5):956-64;
13. Elbes D, Denost, Q, Laurent C, Trillaud H, Rullier A, Quesson B. A Preclinical Study of in vivo MR-guided Bubble Enhanced Heating in Pig Liver; Ultrasound Med Biol. Ultrasound Med Biol. 2013; 39(8):1388-97;
14. Kim YS, Trillaud H, Rhim H, Lim HK, Mali W, Voogt M, Barkhausen J, Eckey T, Köhler MO, Keserci B, Mougenot C, Sokka SD, Soini J, Nieminen HJ. MR thermometry analysis of sonication accuracy and safety margin of volumetric MR imaging-guided high-intensity focused ultrasound ablation of symptomatic uterine fibroids. Radiology. 2012 Nov;265(2):627-37;
15. Voogt MJ, Trillaud H, Kim YS, Mali WP, Barkhausen J, Bartels LW, Deckers R, Frulio N, Rhim H, Lim HK, Eckey T, Nieminen HJ, Mougenot C, Keserci B, Soini J, Vaara T, Köhler MO, Sokka S, van den Bosch MA. Volumetric feedback ablation of uterine fibroids using magnetic resonance-guided high intensity focused ultrasound therapy. Eur Radiol. 2012 Feb;22(2):411-7;
16. Mougenot C, Köhler MO, Enholm J, Quesson B, Moonen C. Quantification of near-field heating during volumetric MR-HIFU ablation. Med Phys. 2011;38(1):272-82;
17. Quesson B, Laurent C, Maclair G, de Senneville BD, Mougenot C, Ries M, Carteret T, Rullier A, Moonen CT. Real-time volumetric MRI thermometry of focused ultrasound ablation in vivo: a feasibility study in pig liver and kidney. NMR Biomed. 2011;24(2):145-53.;
18. Köhler MO, Denis de Senneville B, Quesson B, Moonen CT, Ries M. Spectrally selective pencil-beam navigator for motion compensation of MR-guided high-intensity focused ultrasound therapy of abdominal organs. Magn Reson Med. 2011;66(1):102-11.

Patents

1. Marquet F., Bour P., Vaillant F. and Quesson B. Méthode de contrôle d'une zone ciblée du cœur, méthode d'ablation d'une zone ciblée du cœur, systèmes associés. Dossier n°21876, date de dépôt prioritaire: 3 Sep 2014;
2. Marquet F., Bour P., Vaillant F., Dubois R. and Quesson B. Méthode de contrôle pour la calibration d'un faisceau ultrasonore focalisé pour la stimulation cardiaque, méthode de stimulation cardiaque, systèmes et dispositifs associés. Dossier n°21830, date de dépôt prioritaire: 3 Sep 2014.

More than **10** invited lectures at national and international conferences

More than **30** Communications at international peer-reviewed conferences

B.22 Work package "new sequences" – Coordinator: Sylvain Miraux (RMSB)

Objectives of the WP: The objective of the WP2 is to develop new MRI sequences in order to push the limits of the technique in terms of spatial and temporal resolutions. It is also intended to create imaging sequences for improving the measurement of quantitative parameters. The MRI methodology and particularly sequence development is a historical theme in Bordeaux. It brings together an important number of researchers involved in both WP1, 2 and 3.

Research project: Three research projects were funded in WP 2:

- The NewFISP project in 2012, 250 k€ (PI: S. Miraux)
- The HR-DTI project in 2012, 130 k€ (PI: B Hiba)
- The MDMRI project in 2016, 49.6 k€ (PI: B Hiba)

Scientific results:

NewFISP:

The NewFISP project has focused on developing new ultra-fast MRI sequences for cardiovascular imaging and oncology. The originality of the project is based on the development of non-Cartesian (spiral and radial) k-space encoding methods. These methods were coupled with a pseudo-random projections distribution as well as synchronization or self-synchronization methods. Consequently, it was possible to visualize phenomena inaccessible by/with MRI until now (such as visualization of the blood flow in the Circle of Willis in the brain) and to measure 3D parameters on moving organs like the heart (T1 measurement on the heart in 3D).

This project also leads to purely methodological developments with the creation of 3D hybrid radial / spiral sequences. This new method could lead to numerous applications in neuroimaging or real-time imaging.

This project led to nine publications in international peer-reviewed journals.

Project weaknesses: The sequences developed during this project have for the most of them been developed at high magnetic fields for pre-clinical imaging of the small animals and have not yet resulted in publications in humans.

Project highlights: The new sequences and reconstruction algorithms have been transferred or are being developed on low-field imaging systems used for the WP1 PDN and on clinical imaging systems dedicated to interventional imaging for the WP2 in collaboration with the teams of E Thiaudiere and B Quesson, respectively.

HR-DTI:

An optimal diffusion MRI acquisition sequence was set up to acquire spatially highly resolved data (1.2 mm isotropic). Two super-resolution denoising and reconstruction algorithms, adapted to MRI diffusion, have been developed, optimized, validated for the analysis of the anatomical connectivity of the human brain.

Some of the highest spatial resolutions (up to 400 isotropic microns) achieved in this field have been reached due to the developed methodology. Validations on human brain demonstrate an interest in using these methods for clinical applications.

The project has led to 13 publications in international peer-reviewed journals mostly in the field of image processing.

Project weaknesses: The project did not really contribute to the development of new MRI sequences.

Highlights of the project: The algorithms developed were used to pre-process data from the two cohorts of Bordeaux (stroke and multiple sclerosis). The results of this work show that the denoising and super-resolution algorithms developed in this project are robust enough to be used in clinical routine. Siemens is involved in the development of this project with the funding of a PhD student.

MDMRI:

The project has just begun. The results are encouraging.

Research achievements

B.23 Work package "DNP" - Coordinator: Eric Thiaudiere (RMSB)

a) In Situ DNP

› General Objectives of the WP#3

The WP#3 aims at developing cutting-edge methods in order to compensable for the intrinsic lack of sensitivity in NMR/MRI experiments. Two stategies are considered : a) the use of hyperpolarized Nuclei such as 13C (Dissolution DNP, Dr Y. Crémillieux) and b) in situ DNP (dynamic nuclar polarization). The latter only will be described here.

› TRAILDNP Objectives

The goal is to deveop an MRI strategy in order to unveil proteolysis in vivo, chiefly abnormal proteolysis that can be associated with inflammatory or cancer diseases. The project is an upstream project in the sense that methodological approaches and their validation in vivo are limited to the preclinical area (mouse imaging).

› TRAILDNP Methods

In situ DNP-MRI is performed at 0.194T using a microwave cavity operating at 5.43 GHz for unpaired electron excitation of stable nitroxides. Nitroxide probes are synthesized in the UMR 7273 and further developed and characterized in the UMR 5536. The specificity of DNP enhancements are brought about in two ways : either nitroxide-labeled protein cleaveage or through the use of frequency shifting nitroxides. MRI is performed in 3D.

› TRAILDNP Results

Since 2011 the following achievement were produced :

- 3D DNP-MRI in vivo on-demand in mice without issues of heating nor nitroxide toxicity;
- proof of concept of DNP-MRI of macromolecular proteolysis in vitro and in vivo in mice;
- proof of concept in vitro of a new class of nitroxides as theranostic agents;
- proof-of-concept in vitro and in vivo of a new kind of enzymatically-shifing nitroxides for MRI of proteolysis.

› TRAILDNP Perspectives

The aim is now to produce peptides which can be grafted to nitroxides in order to bring specificity in protease imaging. Up to now, elastase-cleavable substrate are about to be grafted onto frequency-shifting notroxide. In the mean time a new MRI system operating at 0.194 T was installed in 2016 and the OMRI setup was moved from the former system to the new one, thus involving a number of preliminary tests and possible delays. A new PhD student has been enrolled on the 1st of december of 2016 in order to make possible the continuing of the project.

b) Dissolution DNP (dDNP)

› Coordinator :

Dr. Yannick Crémillieux, Equipe IRM Moléculaire, Institut des Sciences Moléculaires - UMR 5255 - CNRS Université de Bordeaux

› Objectives

The aim is to apply Dynamic Nuclear Polarization (DNP) techniques generating hyperpolarized metabolites. These hyperpolarized substrates, their products and reaction intermediates can be detected and followed in vivo for probing cell metabolism. The primary objective concerns the investigation of tumor metabolism for diagnostic, grading and evalution of treatments. It is envisioned as well to apply dDNP for investigating brain (neuronal and glial) metabolism.

› Methods

The research program is based on the use of a home-built dissolution DNP system. The research program includes the implementation of original approaches for the delivery of hyperpolarized substrates. This covers the use of microdialysis probes and the manufacturing of sensitive NMR microcoils for local probing of the cell metabolism.

› Results

The following results have been achieved:

- Installation of the dissolution DNP apparatus in Bordeaux University;
- Dissolution and detection of hyperpolarized metabolites in pre-clinical MRI;
- Manufacturing of NMR microprobes for local detection of metabolites;
- NMR detection of metabolites in µL volume in brain and glioma.

› dDNP Perspectives

Next steps include the design of implantable NMR microprobes and the controlled and local delivery of hyperpolarized compounds in healthy brain and tumor environment. One of the overall objective is the development of MRS and MRI protocols for assessing the efficacy of anti-tumoral treatments. The dissolution DNP system will be localized in the future in the IBIO institute in the vicinity of clinical research whole-body systems.

■B.24 Work package "tracers and constrast agents" - Coordinators: Mireille Blanchard-Desce (ISM), Philippe Fernandez (INCIA)

The purpose of the Work Package 4 is to develop smart imaging agents in the framework of projects **from benchside to bedside**, particularly in the areas of oncology, cardiology and neurology. It involves an interdisciplinary approach which relies on the design of novel contrast agents having unique features (in terms of specificity/selectivity/sensitivity/multimodality) and/or the development of efficient tools to synthesize new molecules or modified biomolecules and to use them as tracers and contrast agents. In this framework, projects involving different/complementary imaging techniques (PET, MRI, MPI, FMT, NIRF) have been funded. Most approaches involve smart targeting approaches.

The WP4 has actually funded 8 research projects for a total budget of **1018 k€ since the end of 2011**.

- **PIAF** (164 k€ since 2011)
  The project will firstly establish the interest of the αvβ3 integrin imaging by PET imaging, by conceiving and achieving the synthesis of an original 18F-RGD radiotracer, then experimenting it on a murine tumor model of melanoma. The research project was completed in 2016 and resulted in several publications and communications: Cold syntheses of radiotracers have been completed. The development of the radiolabeling conditions was carried out and optimized for two molecules and the radiotracers were prepared. The small animal tests were completed for the first generation molecule.

- **IMMELAPT** (250 k€ since 2012)
  ended in 2016 and concerned the synthesis of innovative aptamers recognizing a human protein (MMP9) overexpressed in tumors, then their labelling for ex vivo and in vivo imaging. Starting from an aptamer previously targeting the human MMP-9 -a protein that is overexpressed in tumors, several derivatives of this aptamer have been synthesized and characterized, then converted into imaging probes, for different modalities. Ex vivo Human melanoma samples have been imaged. Finally, an original dimer was developed (PEG chain and aptamers carrying DOTA ligand) but unfortunately the radiolabelling process of this dimer was no successful.

- **SUPSIFLU** (130 k€ since 2013)
  aims to develop a new 18F labeling strategy on solid support that may be applicable to a wide range of biological molecules. Synthesis of the di-tert-butylsilyl-imidazole 3 platform has been improved for more reproducible yields. This was then combined with various biomolecules of biological interest which will soon be fluorinated. In order to upgrade to the supported version, an initial pathway to substitution of imidazole 3 has been studied (see «prospects» in the 2015 report). Unfortunately, the first strategy was unsuccessful. A new strategy of post-functionalization is currently under study and seems much more promising.

- **PRITOR** (90 k€ since 2013)
  Receptors of some regulatory peptides can be highly expressed in various human tumors, thus offering the opportunity of a specific molecular imaging with radiolabeled peptides. Advantageous pharmacological and pharmacokinetic properties as well as easy radiolabeling procedures make peptides attractive molecular tools for molecular imaging of antibodies and their derivatives. Radiolabeled analogs of somatostatin receptors for the imaging of neuroendocrine tumors have been developed and a pilot clinical study of 19 patients with TNE has been conducted. Today, a study on the expression of somatostatin receptors in Hodgkin lymphomas is underway. On the other hand, we have characterized the expression of GRPR in multiple primary tumors of breast cancers and metastatic lymph nodes and studied the correlations between this expression and various clinical and biological parameters. Finally, the expression of NTR1 is studied in various tumors to provide the molecular rational necessary for the development of neurotensin and neuropeptide-Y analogs. The selection of innovative radioisotopes for prospective internal vectorized radiotherapy is also under study.

- **NEPMIP** (35 k€ since 2015)
  The objective of this project is to develop a nanoemulsion platform dedicated to Magnetic Particles Imaging (MPI). In this context magnetic oil-in-water nanoemulsions (NE) have been developed. These oily droplets were loaded with superparamagnetic iron oxide nanoparticles (SPION) and functionalized with atheroma specific ScFv-Fc TGE4-2C antibody. Nanoemulsions including SPION were assessed for MRI and MPS, confirming the great potential of NE as new translational contrast agent. For MRI, unsurprisingly for superparamagnetic agents, transverse relaxivities r2 and r2* increased with the loaded SPION sizes. MPS assays reveal that the signal increased with the size of the NPs loaded into the NE. The formulations ability to selectively bind the atheroma plaque was evaluated both in vitro and ex vivo on animal models of atherosclerosis. Antibody functionalized NE showed a specific labeling of the atheroma plaque, supporting that this NE platform was able to selectively image atherosclerosis for diagnosis purpose.

Research achievements

› **TARGLIN** (150 k€ since 2015)
The objective of the project is to develop peptide-based nanoparticles for addressing siRNAs targeting specific gene in glioblastoma and tumor microenvironment in a mouse xenograft model. In vivo imaging will be used to determine peptide-based nanoparticles (PBN) bio-distribution, specific targeting and tumor growth reduction. This work included new molecular cloning, cell line generation and in vivo testing. The new cell line is currently available for in vivo testing. To determine cell targeting of PBN in vivo, orthotopic brain tumors has been generated and PBN injected i.v. Evidence of fluorescence from PBN was observed on tumor slice but fluorescence was lost during the antigen retrieval process. Current experiments are trying to establish protocols for different cell-type identification by immuno-histochemistry without altering fluorescent signal from PBN. Together with Fluc and Nluc expression, intracerebral tumors also expressed a new Near infrared protein called iRFP that allowed for fluorescent molecular tomography (FMT) imaging, for tumor localization and for absolute quantification. Performances of iRFP for brain tumors has been published (Genevois et al, 2016). As part of the screening program the Montpellier team has synthesized a new PBN containing siRNA called W3. This new nanoparticules was found highly efficient for lucF inhibition in vitro and has been assayed in vivo on sub-cutaneous tumors.

› **FITTING** (49 k€ in 2016)
concerns the synthesis of an 18F-labeled cycloheptyne probe to empower the bioorthogonal ligation technology with PET capabilities for translational applications.
In order to introduce on the probe the 18F-element required for PET imaging of polysialic acid, a novel Si-containing cycloheptyne probe has been designed and synthesized. For stability purpose, the strained alkyne functionality has been masked as a cyclopropenone moiety that can be deprotected by simple UV irradiation. Accordingly, the cyclopropenone-protected Si-cycloheptyne was produced in a concise two-step approach and confirmation of the structure was established by X-Ray crystallography. The photochemical decarbonylation showed to be efficient under irradiation at 350 nm. The photochemical decarbonylation was carried out in the presence of azides (aromatic, benzylic and aliphatic) to trap in-situ the triazole adducts in quantitative yields.

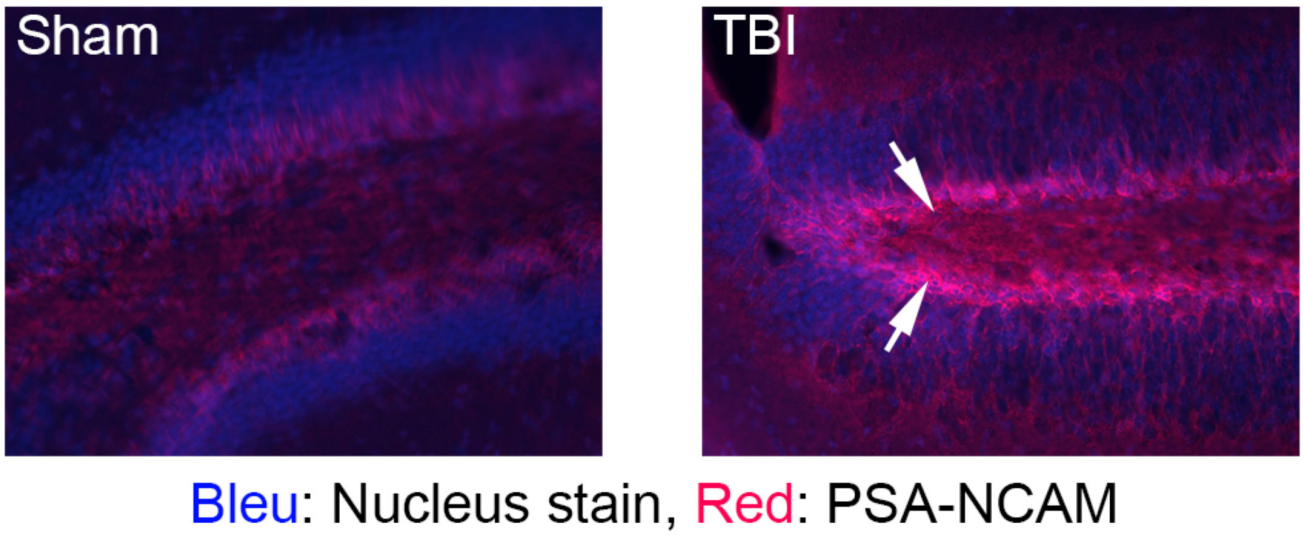


Figure. PSA expression after TBI. TBI induced an increase in PSA expression in the hippocampus xx days after impact.

› **NANOMULTIMAG** (150 k€ in 2016)
proposes a strategy based on biocompatible nanoemulsions (NE developed by ARNA-U1212 INSERM partner) incorporating two complementary nanomaterials in a convergent manner: some iron oxide nanoparticles (SPION, elaborated by ICMCB-CNRS partner) that can be analyzed by MRI and MPI and NIRF-emitting ultra-bright nanodots dedicated to one-photon or two-photon fluorescence microscopy, thus providing complementary modalities in terms of sensitivity, imaging scale and resolution (from microscopic to in vivo imaging). The biological question that guided the design of this trimodal agent is the detection of micrometric atherosclerotic lesions, which develop in the intima of medium and large arteries. Highly sensitive and specific nano-objects are necessary to image these dangerous lipid-rich plaques. To construct adequate sensitive and specific nano-objects, we have to face two issues: the labelling with biomarkers specific to the pathology and the use of biocompatible carriers able to vehicle the targeted imaging probes to the micrometric lesions.
The RMSB –UMR5536 partner has characterized human antibodies specific to biomarkers of the pathology, which were reformatted as ScFv-Fc fragments (an original antibody format that associates two scFv (single-chain variable fragment: VH-linker-VL) to the Fc portion of human IgG1). The antibodies with the highest signal in the aorta will be studied in vivo after grafting with HIFONS fluorophores, which are ultrabright NIR-emitting biocompatible molecular-based nanoparticles designed in ISM-UMR5255 partner. The joint incorporation of two types of nanoparticles (SPION and nanodots) into the same biocompatible nanovehicle has been achieved leading to multimodal contrast agents exhibiting unprecedented brightness (red to NIR fluorescence) and large MRI signals. Their surface functionalization with human antibodies and use as multimodal agents is under study.

■B.25 Work package "biological bioimaging markers" - Coordinator: Gisèle Clofent-Sanchez (RMSB)

WP5 projects cover Neurology, Oncology, Bronchial and Cardio-Vascular diseases on two main scopes.

› Find-Fight-Follow : targeting and Imaging biomarkers to predict and follow the course of pathologies and provide personalized treatment
› Development of novel multimodal imaging modalities from diagnostic to theranostic

Learning from physiological, cellular or molecular events occurring in pathologies to predict disease progression, prognosis and evaluate therapeutic intervention are the major axes of WP5.

Each project fosters the development of translational research from the targeting of a physiological process, a cell or a molecule involved in pathologies to the implementation of the focused bio-imaging in humans.

Biomarkers in Neurology

1- Project « Longterm neurovascular unit changes after mild traumatic brain injury: potential biomarker & Vasc-TBI »
PI : Jérome Badaut

Mild traumatic brain injury (mTBI) is known to induce long-term brain disorders with increased risk of neurodegenerative diseases and reductions in patient lifespan. The working hypothesis is that TBI induces long-term phenotypic changes of the neurovascular unit (NVU) associated with the emergence of cognitive dysfunctions.

Current scientific activities and results:
Vasc-TBI aims to evaluate vascular changes after mild TBI in a new juvenile TBI model: CHILD©, for Closed Head Injury Longterm Dysfunction. The induced changes in the neurovascular compartment in the white matter tract are associated with chronic changes with decrease of fraction anisotropy values after 1month with anxiety as revealed by DTI. MRI structural changes will be further evaluated within 3 cohorts of mTBI patients: soccer players with repetitive headings, patient with mild TBI from the emergency room and age/sex matched control group.

Relevance with WP5 TRAIL funding :
This translational project spans from ex vivo studies in rodent model to clinical monitoring of mTBI patients seeking care at Bordeaux CHU. This project highlights the importance of following cerebral perfusion as a new biomarker in parallel to the behavioural evaluation.

Research achievements

2- Project "Grey matters! Toward a better understanding of grey matter alteration and cognitive deficit associated with multiple sclerosis" GM-COG ;

PI: Thomas Tourdias and Aurélie Ruet

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the CNS characterized by perivascular infiltration of lymphocytes and macrophages, which in turn promote demyelination and axonal injuries. The involvement of grey matter (GM) regions was acknowledged in early pathology studies. GM-COG aims to elucidate the mechanisms that trigger GM alteration at the early stage of Multiple Sclerosis by implementation of reliable in vivo methods to quantify and to monitor the most eloquent GM areas in terms of cognitive impact.

Current scientific activities and results:

By performing qPCR analyses on auto-immune encephalomyelitis (EAE) mice, first results were obtained acknowledging the role of complement in the pathological cross-talk between glial cells and hippocampal dendrites with consequences in memory deficit. Advanced in vivo diffusion imaging named NODDI (Neurite Orientation Dispersion and Density Imaging) was optimized to capture some of these features in vivo non-invasively. T lymphocytes called circulating T follicular helper (cTfh) potentially involved in a primary meningeal inflammation are under study on patients and healthy controls.

Relevance with WP5 TRAIL funding :

Identifying a correlate of the molecular and functional mechanisms with non-invasive in vivo imaging in EAE mice could then foster future translation in MS patients using the same MRI methodology combined to immunological approaches. This opens exciting opportunity to identify human biomarker reflecting spatio-temporal cellular modifications in early disease.

3- Project "Imaging Biomarkers of experimental and clinical neuroinflammation" IBIO-NI

PI Bruno Brochet

IBIO-NI proposes to study which MRI parameters could be used as biomarkers to predict cognitive deficiencies (mainly information processing speed (IPS) and memory) occurring at the early stages of MS (high-risk clinically isolated syndromes (CIS)).

Current scientific activities and results:

(1) Lateral diffusion along the astrocyte membrane of aquaporin 4 (AQP4) and its consequence on synaptic activity. Two isoforms of AQP4 highly mobile along the membranes were identified as well as how diffusion of AQP4 is modified in pathological conditions.

(2) Microscopic water movements within cells during focal brain inflammation using Diffusion Tenser Imaging (DTI). DTI was developed and successfully used to obtain early and non-invasive biomarkers of hippocampus lesion in EAE mouse model induced by IL-ß. NODDI was compared to DTI.

(3) Mechanisms of cognitive impairment in MS using DTI. The first MRI analysis (3D-T1 weighted imaging and DTI) of CIS patients suggested that (i) an early neuropathological process contributing to memory deficit occurs within the hippocampus in MS; (ii) the atrophy of specific cerebellar lobules is associated with reduced working memory and IPS.

(4) Large cohorts of MS patients (OFSEP) and controls (I-Share) to validate MRI markers. The OFSEP CIS cohort started in January 2016. 58 CIS patients were included so far in 10 different centers in France.

Relevance with WP5 TRAIL funding :

IBIO-NI involves teams from bench to bed with neuroscientists carrying basic research and clinicians directly interacting with patients. The research started from the « cell » and extended to « population »

4- Project "Translational study of the cerebral substrates involved in pathological fear recovery" TRANSFEAR

PI:Melissa Bonnet

Anxiety Disorders including post-traumatic stress disorders (PTSD) are the most common mental disorders occurring early in life and at risk factors for other mental disorders later in life such as affective disorders and substance abuse disorders.

Current scientific activities and results:

TRANSFEAR aims at identifying the changes in functional connectivity occurring in medial prefrontal regions and amygdala involved in fear and extinction learning during fear behaviour using electrophysiological recordings in rodents and functional Magnetic Resonance Imaging (fMRI) technique in humans. In mice, prefrontal-amygdala neuronal coherence was observed during extinction and retrieval sessions only in low fear group. High theta coherence during extinction learning was found to predict low fear recovery in mice. In humans, amygdala was found functionally connected during extinction with the prefrontal regions only for the low fear group. The same prefrontal regions were strongly correlated with greater post-extinction REM sleep ratio. Prefrontal activation during extinction was found to predict extinction consolidation in humans.

Relevance with WP5 TRAIL funding :

Elucidating the neural mechanisms mediating pathological fear recovery should further suggest novel therapeutic strategies for psychiatric conditions characterized by a high propensity to relapse such as PTSD.

5-Project "Role of astrocytic lactate in neuronal metabolism: implication during brain activation and neuroprotective effect in neonate cerebral hypoxia". InNES

PI: Anne-Karine Bouzier-Sore

InNES main aim was initially to understand the role of lactate in brain metabolism and its importance as a neural substrate, in addition to glucose, during brain activation. Considering the crucial role of lactate in the brain, the project turns out to study the neuroprotective effect of lactate after hypoxia-ischemia.

Current scientific activities and results:

Results clearly show a neuroprotective effect of lactate after hypoxia-ischemia in rat pups. This neuroprotection was completely abolished with oxamate, an inhibitor of the lactate dehydrogenase enzyme, indicating that the neuroprotection of lactate acts through the metabolic pathway. Analyses on metabolism and molecular targeting of lactate are done using NMR HR-MAS spectroscopy and 7T MRI in vivo imaging.

Relevance with WP5 TRAIL funding :

InNES is a translational research with transfer of new knowledge on the role of astrocytic lactate as an efficient neuronal substrate during brain activation to a pathological situation: brain hypoxia in neonates. It is done in close collaboration with Luc Pellerin, a pioneer in the astrocyte-neuron lactate shuttle theory (Excellence Research Chair in Bordeaux in 2017) and Jean-François Chateil, radiologist at the children hospital in Bordeaux.

Biomarkers in Oncology

Project "Antibody-based fluorescence probe for biopsy guidance of prostate cancer" BIOPSYPROSTAPROBE

PI: Franck Couillaud

Prostatic carcinoma (PCa) is the most common cancer in men and the second cause of cancer-related deaths for North American and European men. Its aggressiveness depends on the extent of the tumor. Early detection can greatly enhance life expectancy. BIOPSYPROSTAPROBE is dedicated to the development of probe for imaging prostate cancer based on a high affinity anti-PSMA antibody scFv fragment.

Current scientific activities and results:

ScFvD2B, labeled using a near-infrared fluorophore and injected to an orthotopic model of prostate cancer, was detected in vivo by fluorescence molecular tomography in the prostate region.

Relevance with WP5 TRAIL funding :

NIR-labeled scFvD2B could thus be developed as a clinical probe for hybrid imaging-guided targeted biopsies, combining echography and fluorescent tomography. A prototype will be available in Bordeaux in 2017. Translational studies on human samples and later on in patients is managed by Prof. N Grenier (Bordeaux CHU).

Biomarkers in bronchial diseases

Project STEAMRI

PI: Gael Dournes

Chronic respiratory diseases such as severe asthma or chronic obstructive pulmonary diseases (COPD) are a major public health problem with an increasing incidence in all industrialized countries. STEAMRI aims to assess the feasibility of whole lung oxygen-enhanced (OE) imaging in humans using MRI with the PETRA sequence for more effective assessment, understanding and appropriate management of lung function.

Current scientific activities and results:

A first work consisted in implementing new modalities of signal acquisition and to reduce the time of acquisition. Acquisition times varying between 3 and 5 minutes with no impact on imaging quality were obtained. The expected total duration of a pre / post 02- enhancement study is thus between 6 and 10 minutes, versus 30 minutes initially. Application to a group of healthy volunteers is the subject of a request submitted to the DCRI in Bordeaux CHU.

Relevance with WP5 TRAIL funding :

The new tools do not require an ionizing acquisition and will enable the diagnosis of fragile people (child, young adult, pregnant women, ...) for many bronchial diseases and the outcome of bronchial changes after treatment. The study of small airway disease in humans will most probably lead to new markers of bronchial diseases.

Research achievements

Biomarkers in Cardiovascular diseases

1-Project "Inflammatory pathways leading to intracranial aneurysm growth" IPALICA
PI: Jérome Berge

Intracranial aneurysm (IA) rupture with subsequent subarachnoid haemorrhage remains a life-threatening medical emergency despite recent diagnostic and therapeutic advances. Through a multidisciplinary approach, this project aims at characterizing inflammatory and metabolic profiles in patients with ruptured or non ruptured IAs.

Current scientific activities and results:
The design of the transcriptomic, metabolomic and histologic approaches is in place with the different teams and the circuit of sampling of aneurysm pieces definitively established. Thanks to the two teams of neurosurgery, 12 pieces of unruptured aneurysms, 22 ruptured and 6 control arteries were harvested. Immunohistochemistry analyzes are ongoing as well as genetic analyses. All the pieces will be analyzed at the same time for the sake of economy and efficiency. The metabolomic study will be conducted at the last step in function of the information obtained from the genetic and histologic analyses.

Relevance with WP5 TRAIL funding :
IPALICA conducted ex vivo on aneurismal biopsies will lead to the characterization of molecular and cellular mechanisms underling this pathology. The final aim is to improve diagnosis and treatment in collaboration with three industrial partners (Microvention, Balt et Penumbra) involved in the field of endovascular treatment of intracranial aneurysms.

2- Project "Molecular IMaging of ATHeroma with HUMan AntiBody" MIMATHUMAB
PI: Gisèle Clofent-Sanchez

Atherosclerosis is identified as the underlying condition for most acute cardiovascular events, such as stroke and infarction. Thus, providing clinicians with reliable and straightforward imaging techniques to identify «vulnerable» patients from the general population appears like the Holy Grail of the cardiovascular field. MIMATHUMAB proposes the use of human antibodies (HuAbs) selected by phage-display in animal models of the pathology to functionalize nanoparticles (NPs) in a site-directed approach.

Current scientific activities and results:
Most of works were conducted with a human antibody specific to the platelet αIIbβ3 integrin for its relevance to detect high-risk atheroma plaques rich in platelets. Site-specific grafting was addressed either by introducing Cysteine or Sortase recognition tags for multi-modality imaging (MRI, fluorescence, or PET). The approach was validated ex vivo by fluorescence and further by MRI in the ApoE-/- mouse model. The specificity of other HuAbs in the pipeline selected by in vivo phage-display is addressed via direct conjugation with NIRF probes for fluorescence imaging before further grafting to multimodal NPs. Adding a therapeutic dimension thanks to the ATHERANOS ANR project, a theranostic approach has been evaluated using Solid Lipid Nanoparticles.

Relevance with WP5 TRAIL funding :
HuAbs recognizing atheroma in animal models and coronary or carotid human sections have the potential to be used from pre-clinical to clinical studies to fulfill a translational approach. MIMATHUMAB was the stepping-stone for many collaborations and further grants with international collaborators as well as firms like LFB Biotechnologies, Brüker and Pacific BioSciences.

■B.26 Work package "mathematic simulation and modeling" - Coordinator: Thierry Colin (IMB)

The work-package « Mathematical modelling » is devoted to the development of innovative mathematical and numerical method to address problems arising in the context of medical imaging, specially for clinical applications. The projects that have been developed in this work-package are jointly leaded on one hand by a team of the core TRAIL partners in digital sciences (LaBRI: laboratory of Computer Science of Bordeaux and IMB: Institute for Mathematics of Bordeaux) and on the other hand by a team of clinicians of Bord eaux University Hospital or of Institut Bergonié. These joined leaderships ensure the development of up-to-date numerical methods that can be validated on high quality clinical data. This is the absolute condition to develop high valued digital tools in the context of medical imaging.

These last years, the projects that have been developed in TRAIL focused on applications in oncology (2), in nephrology(1), pneumology(1) and neurology(2).

1. **Concerning oncology**, the first target was to propose an automatic assessment of radiofrequency ablation margins for the liver including a complete 3D registration procedure. The second project that started 2 years ago deals with the modeling of the response to targeted therapies of patients that are followed with a mix of CT-scans and MRI. The idea is to develop new bio-markers that are built with mathematical models that are parametrized thanks to MRI, CT-scans or PET data.Both projects will be developed industrially by a start-up that will be created locally.

2. The only **nephrology** project deals with the analysis of heterogeneity of MRI maps. The post-processing tools are ready and the project leader is waiting for the collect of data.
3. The **pneumology** project aims at developing a new segmentation tools for the bronchial tree. The project, that is almost completed, will lead to a industrial transfer with Intrasens.
4. The **neurology** projects these last years have been founded by the Labex Brain and CPU but they are fully in the TRAIL dynamics. The first one deals with abnormality detection using sparse-based modeling of brain anatomy: application to Alzheimer's disease. The second one aims to construct an in-vivo ultra-high resolution diffusion MRI platform with application to multiple sclerosis.

All these projects have led (or will lead) to the development of numerical platforms or numerical codes that satisfies the usual standards (systematic use of collaborative development tools, non-regression testing strategy, etc...). This will allow a CE approval as medical device if necessary.

B.27 Work package "cohort imaging methodology" - Coordinator : François Laurent (CRCTB)

The main objectives of TRAIL WP7 is :

1) the development of advanced platforms with automated algorithms for processing large image dataset produced by cohorts;
2) the validation of biomarkers from data extracted from the cohorts analyses.

Five projects have been funded since 2011:

1) **TRAIL and TRACKS** (A population-based probabilistic atlas of white matter tracts of the human brain) is a stem-based tracktography algorithm developed to delineate the association tracts of white matter in the human brain. Two papers have been published before 2016 and a thesis defended at the end of 2015
2) **ABACI** is a neuroanatomical analysis pipeline implemented and used for the MIBRAIN cohort. The tool is currently used for automated identification of bright spots of brain white matter and is currently applied to the cohort MRI-Share and to ongoing cohorts dedicated to study the aging brain. ABACI2 and PACA are extending the ABACI pipeline for processing intrinsic FMRI data, and building a program dedicated to the development of a probability atlas of brain cortical areas, respectively.
3) **ACTE** is a morphofunctional evaluation of corticocerebellar circuits implicated in cognitive brain and functional connectivity. Two papers are currently submitted and under review and 4 scientific presentations of results have been performed in 2016. Collaboration has been developed in order to implements tools for analyzing functional connectivity in aging brain and a thesis on the subject is ongoing.
4) **COBRASCAN** (Quantitative computed tomography for phenotyping COPD within COBRA cohort) is an advanced CT image analysis programs used to analyze in details the morphological changes involved in COPD, i.e. the severity of emphysema, airways dimensions, small airways obstruction and small pulmonary vessels from CT images. The COBRA project directed by INSERM relies on a national cohort of 500 patients suffering from COPD or asthma with the main objective to determine clinical, biological and genetical determinants of the outcome of patients. The hypothesis in COBRASCAN is that a CT quantitative morphological analysis reflecting lung parenchymal destruction (emphysema), bronchial wall remodeling of large and small airways and changes in pulmonary vessels has a significant prognostic impact. The study will specify the role of quantitative CT as a biomarker of COPD, and its position in on-going clinical trials. Phenotyping COPD into appropriate subgroups using is likely to play a role in pharmacological research. Quantitative MRI imaging of lung parenchyma, vessels and bronchi developed by the same research group is linked to the project. So far, the project has been applied to subpopulations participating to COBRA in Bordeaux and lead to several publications dedicated to validation of parts of the project. Inclusions from other centers is currently under analysis.
5) The **ADPP** project objectives are to obtain information on the link between cerebral modifications and the emergence of cognitive symptoms in aging subjects, which characterize the presymptomatic phase of AD, by considering structural (through morphological MRI and diffusion MRI) and functional (through rest fMRI) networks modifications underlying cognitive decline.
Two recruitments have been done, and a thesis began. A pipeline was developed to analyze functional connectivity and statistical analyzes of MRI data are ongoing.

Research achievements

B.3 Scientific communication

B.31 Publications quoting TRAIL

a) 89 publications have been published over the 2011-2016 period :

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP1 - MR Guided HIFU and interventional imaging	MRGHIFU	2016	Non-invasive cardiac pacing with image-guided focused ultrasound, Fabrice Marquet, Pierre Bour, Fanny Vaillant, Sana Amraoui, Rémi Dubois, Philippe Ritter, Michel Haïssaguerre, Mélèze Hocini, Olivier Bernus & Bruno Quesson, Nature Scientific Report, Oct 16	Nature Scientific Reports
		2016	Improved Cardiac Magnetic Resonance Thermometry and Dosimetry for Monitoring Lesion Formation During Catheter Ablation, Valery Ozenne, Solenn Toupin, Pierre Bour, Baudouin Denis de Senneville, Matthieu Lepetit-Coiffe, Manuel Boissenin, Jenny Benois-Pineau, Michael S. Hansen, Souheil J. Inati, Assaf Govari, Pierre Jais, and Bruno Quesson, Magnetic Resonance in Medicine, Jan 2016	Magnetic Resonance in Medicine
		2015	Detection of Brain Tumors and Systemic Metastases Using NanoLuc and Fluc for Dual Reporter Imaging. C. Germain-Genevois, O. Garandeau, F. Couillaud. Mol Imaging Biol (2015)	Mol Imaging Biol
WP2 - New Sequences and new contrast	HRDTI	2016	Non Local Spatial and Angular Matching: Enabling higher spatial resolution diffusion MRI datasets through adaptive denoising, Samuel St-Jean,Pierrick Coupé, Maxime Descoteaux, Medical Image Analysis, March 2016	Medical image analysis
		2016	Automatic thalamus and hippocampus segmentation from MP2RAGE: comparison of publicly available methods and implications for DTI quantification, Erhard Næss-Schmidt, Anna Tietze, Jakob Udby Blicher, Mikkel Petersen, Irene K. Mikkelsen, Pierrick Coupé, José V. Manjón, Simon Fristed Eskildsen, International Journal of Computer Assisted Radiology and Surgery, June 2016	International Journal of Computer Assisted Radiology and Surgery
		2016	Fasudil treatment in adult reverses behavioural changes and brain ventricular enlargement in Oligophrenin-1 mouse model of intellectual disability, Hamid Meziane, Malik Khelfaoui, Noemi Morello, Bassem Hiba, Eleonora Calcagno, Sophie Reibel-Foisset, Mohammed Selloum, Jamel Chelly, Yann Humeau, , Fabrice Riet, Ginevra Zanni, Yann Herault, Thierry Bienvenu, Maurizio Giustetto and Pierre Billuart, Human Molecular Genetics, May 2016	Human Molecular genetics
		2016	VolBrain: An Online MRI Brain Volumetry System, José V.Manjón and Pierrick Coupé, Frontiers in Neuroinformatics, July 2016	Frontiers in Neuroinformatics
		2015	MRI Noise Estimation and Denoising Using Non-local PCA, J. V. Manjon, P. Coupé, A. Buades. Medical image analysis, 22(1): 35-47, 2015.	Medical image analysis
		2015	NABS: Non-local Automatic Brain Hemisphere Segmentation. J. E. Romero, J. V. Manjon, J. Tohka, P. Coupé, M. Robles. Magnetic Resonance Imaging, 33(4): 474-484, 201	Magnetic Resonance Imaging
		2015	Rotation-invariant multi-contrast non-local means for MS lesion segmentation. N. Guizard, P. Coupé, V. Fonov, J. V. Manjon, A Douglas, D. L. Collins. Neuroimage: Clinical, 8: 376-389, 2015.	Neuroimage: Clinical

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP2 - New Sequences and new contrast	HRDTI	2015	An Optimized PatchMatch for Multi-scale and Multi-feature Label Fusion. R. Giraud, V-T. Ta, N. Papadakis, J. V. Manjón, D. L. Collins, P. Coupé and ADNI. NeuroImage 2015	NeuroImage
		2015	Detection of Alzheimer's Disease Signature in MR Images Seven Years Before Conversion to Dementia: Toward an Early Individual Prognosis. P. Coupé, V. S. Fonov, C. Bernard, A. Zandifar, S. F. Eskildsen, C. Helmer, J. V. Manjón, H. Amieva, J-F. Dartigues, M. Allard, G. Catheline, D. L. Collins, and ADNI. Human Brain Mapping, 2015	Human Brain Mapping
		2015	Non-local means inpainting of MS lesions in longitudinal image processing, Nicolas Guizard*, Kunio Nakamura, Pierrick Coupé, Vladimir S. Fonov, Douglas L. Arnold, D L. Collins, Frontiers In Neuroscience, nov 2015	Frontiers in Neuroscience
		2014	Anatomically Constrained Weak Classier Fusion for Early Detection of Alzheimer's Disease. Mawulawo Komlagan, Vinh-Thong Ta, Xingyu Pan, Jean-Philippe Domenger, D. Louis Collins, Pierrick Coupé, and the Alzheimer's Disease Neuroimaging Initiative. Machine Learning in Medical Imaging, pages 141-148, 2014.	Machine Learning in Medical Imaging
		2014	Optimized PatchMatch for Near Real Time and Accurate Label Fusion. Vinh-Thong Ta, Rémi Giraud, D. Louis Collins, and Pierrick Coupé. MICCAI'14, 105-112, 2014.	MICCAI'14
		2013	Collaborative patch-based super-resolution for diffusion-weighted images. Pierrick Coupé, José V. Manjón, Maxime Chamberland, Maxime Descoteaux, Bassem Hiba. NeuroImage 83 (2013) 245–261	NeuroImage
		2013	Diffusion weighted image denoising using overcomplete local PCA. José V. Manjon, Pierrick Coupé, Luis Concha, Antonio Buades, D. Louis Collins, Montserrat Robles. PLoS One Sept 2013,Volume 8, Issue 9	PLoS One
	NEWFISP	2016	Fast 3D Ultrashort Echo-Time Spiral Projection Imaging Using Golden-Angle: A Flexible Protocol for In Vivo Mouse Imaging at High Magnetic Field; Charles R Castets, William Lefrançois, Didier Wecker, Emeline J Ribot, Aurelien J Trotier, Eric Thiaudiere, Jean-Michel Franconi, and Sylvain Miraux*, Magnetic Resonance in Medicine, May 2016	Magn Reson Med
		2016	USPIO-Enhanced 3D-Cine Self-Gated Cardiac MRI Based on a Stack-of-Stars Golden Angle Short Echo Time Sequence: Application on Mice With Acute Myocardial Infarction, Aurelien J. Trotier, PhD, Charles R. Castets, MSc, William Lefrancois, PhD, Emeline J. Ribot, PhD, Jean-Michel Franconi, PhD, Eric Thiaudiere, PhD, and Sylvain Miraux, PhD*, Journal of Magnetic Resonance Imaging, jan 2016	J Magn Reson Imaging
		2015	Free-breathing 3D diffusion MRI for high-resolution hepatic, metastasis characterization in small animals, Emeline J. Ribot, Aurelien J. Trotier, Charles R. Castets, Benjamin Dallaudiere, Eric Thiaudiere, Jean-Michel Franconi, Sylvain Miraux, Clin Exp Metastasis, Nov 2015	Clin Exp Metastasis
		2015	Fast and robust 3D T1 mapping using spiral encoding and steady RF excitation at 7T: application to cardiac manganese enhanced MRI (MEMRI) in mice. C. R. Castets, E. J. Ribot, W. Lefrançois, A. J. Trotier, E. Thiaudière, JM Franconi and S. Miraux. NMR in Biomedicine, mars 2015	NMR in Biomedicine

Research achievements

publications published over the 2011-2016 period :

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP2 - New Sequences and new contrast	NEWFISP	2015	Positive contrast high-resolution 3D-cine imaging of the cardiovascular system in small animals using a UTE sequence and iron nanoparticles at 4.7, 7 and 9.4 T, A. J. Trotier, W. Lefrançois, K. Van Renterghem, JM Franconi, E. Thiaudière and S. Miraux, Journal of Cardiovascular Magnetic Resonance (2015)	Journal of Cardiovascular Magnetic Resonance
		2015	Water Selective Imaging and bSSFP Banding Artifact Correction in Humans and Small Animals at 3T and 7T, Respectively; E. J. Ribot, D. Wecker, A. J. Trotier, B. Dallaudière, W. Lefrançois, E. Thiaudière, JM Franconi, S. Miraux, PLOS ONE, 2015	PLoS One
		2014	Self-gated bSSFP sequences to detect iron-labeled cancer cells and/or metastases in vivo in mouse liver at 7 Tesla. E. J. Ribot, T. J. Duriez, A. J. Trotier, E. Thiaudiere, JM Franconi, and S. Miraux. J Magn Reson Imaging. June 2014	J Magn Reson Imaging
		2014	Time-resolved TOF MR angiography in mice using a prospective 3D radial double golden angle approach. A. J. Trotier, W. Lefrançois, E. J. Ribot, E. Thiaudiere, JM Franconi, and S. Miraux. Magn Reson Med. 2014 Mar 10.	Magn Reson Med
WP3 - Dynamic Nuclear Polarization	ONCOFLUX	2016	MR imaging, targeting and characterization of pulmonary fibrosis using intra-tracheal administration of gadolinium-based nanoparticles, Nawal Tassali, Andrea Bianchi, François Lux, Gérard Raffard, Stéphane Sanchez, Olivier Tillement and Yannick Crémillieux, Contrast Media and Molecular Imaging, May 2016	Contrast Media Mol Imaging
		2016	In vivo online magnetic resonance quantification of absolute metabolite concentrations in microdialysate, Stefan Glöggler, Silvia Rizzitelli, Noël Pinaud, Gérard Raffard, Vanessa Zhendre, Véronique Bouchaud, Stéphane Sanchez, Guillaume Radecki, Luisa Ciobanu, Alan Wong, Yannick Crémillieux, Nature Scientific Reports, Nov 2016	Nature Scientific Reports
	TRAILDNP	2015	Enzymatically Shifting Nitroxides for EPR spectroscopy and Overhauser-Enhanced Magnetic Resonance Imaging, G. Audran, L. Bosco, P. Bremond, JM Franconi, N. Koonjoo, S. Marque, P. Massot, P. Mellet, E. Parzy, and E. Thiaudiere, Angew. Chem. 2015, 127, 1–7	Angewandte Chemie
		2014	In vivo Overhauser-enhanced MRI of proteolytic activity. Koonjoo N, Parzy E, Massot P, Lepetit-Coiffé M, Marque SR, Franconi JM, Thiaudiere E, Mellet P. Contrast Media Mol Imaging. 2014 Sep;9(5):363-71.	Contrast Media Mol Imaging
		2014	Alkoxyamines: toward a new family of theranostic agents against cancer. Moncelet D, Voisin P, Koonjoo N, Bouchaud V, Massot P, Parzy E, Audran G, Franconi JM, Thiaudière E, Marque SR, Brémond P, Mellet P. Mol Pharm. 2014 Jul 7;11(7):2412-9.	Mol Pharm
		2013	Overhauser-enhanced MRI of elastase activity from in vitro human neutrophil degranulation. E. Parzy, V. Bouchaud, P. Massot, P. Voisin, N. Koonjoo, D. Moncelet, J.M. Franconi, E. Thiaudiere, and P. Mellet, PLoS One. 8(2) 2013	PLoS One
WP4 - Tracers and contrast agents	IMMELAPT	2016	Ex Vivo and In Vivo Imaging and Biodistribution of Aptamers Targeting the Human Matrix MetalloProtease-9 in Melanomas, David Kryza*, Frédéric Debordeaux, Laurent Azéma, Aref Hassan, Olivier Paurelle, Jürgen Schulz, Catherine Savona-Baron, Elsa Charignon, Pauline Bonazza, Jacqueline Taleb, Philippe Fernandez, Marc Janier, Jean-Jacques Toulmé, PlosOne, Feb 2016	PLoS One

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP4 - Tracers and contrast agents	NANOMULTI-MAG	2016	In vitro imaging of b-cells using fluorescent cubic bicontinuous liquid crystalline nanoparticles; V. Miceli, V. Meli, M. Blanchard-Desce, T. Bsaibess, M. Pampalone, P. G. Conaldi, C. Caltagirone, M. Obiols-Rabasa, J. Schmidt, Y. Talmon, A. Casu*, and S. Murgia*, RCS Advances, June 2016	RCS Advances
		2016	Z-Shaped Pyrrolo[3,2-b]pyrroles and Their Transformation into p-Expanded Indolo[3,2-b]indoles, Rafał Stezycki,Marek Grzybowski, Guillaume Clermont, Mireille Blanchard-Desce* and Daniel T. Gryko*, Chemistry a European Journal, Feb 2016	Chemistry a European Journal
		2016	Bright Electrogenerated Chemiluminescence of a Bis-Donor Quadrupolar Spirofluorene Dye and Its Nanoparticles; Haidong Li, Jonathan Daniel, Jean-Baptiste Verlhac, Mireille Blanchard-Desce,* and Neso Sojic*, Chemistry a European Journal, July 2016	Chemistry a European Journal
	PIAF	2015	General Last-Step Labeling of Biomolecule-Based Substrates by [12C], [13C], and [11C] Carbon Monoxide. Thomas Cornilleau, Hélène Audrain, Aude Guillemet, Philippe Hermange and Eric Fouquet. Org. Lett. 2015, 17, 354–357	Org Letters
		2013	Pd°-catalyzed methyl transfer on nucleosides and oligonucleotides envisaged as a PET tracer E. Fouquet et al. Molecules, 2013, 18, 13654-13665.	Molecules
		2012	[18F]Si-RiboRGD : the winning combination. From the design and the synthesis to the imaging of avb3 integrins in melanoma tumors. E Amigues, J Schulz, M Szlosek-Pinaud, P Fernandez, S Silvente-Poirot, S Brillouet, F Courbon and E Fouquet, ChemPlusChem 2012, 77, 345-349.	ChemPlusChem
	PRITOR	2016	Dose Deposits from 90Y, 177Lu, 111In, and 161Tb in Micrometastases of Various Sizes: Implications for Radiopharmaceutical Therapy. Hindié E, Zanotti-Fregonara P, Quinto MA, Morgat C, Champion C., J Nucl Med. 2016 May	journal of nuclear medicine
		2016	Comparison between Three Promising ß-emitting Radionuclides, (67)Cu, (47)Sc and (161)Tb, with Emphasis on Doses Delivered to Minimal Residual Disease. Champion C, Quinto MA, Morgat C, Zanotti-Fregonara P, Hindié E. Theranostics. 2016 Jun	Theranostics
		2016	Evaluation of 68Ga-DOTA-TOC PET/CT for the detection of duodeno-pancreatic neuroendocrine tumors in patients with MEN1, Clément Morgat & Fritz-Line Vélayoudom-Céphise & Paul Schwartz & Martine Guyot & Delphine Gay5 & Delphine Vimont & Jürgen Schulz & Joachim Mazère & Marie-Laure Nunes & Denis Smith & Elif Hindié & Philippe Fernandez & Antoine Tabarin, EJNMMI, jan 2016	european journal of nuclear medicine and molecular imaging
		2016	A new class of radiopeptides for PET imaging of neuromedin-B receptor: 68Ga-ranatensin analogs, C. Morgat, R. Varshney, D. Vimont, C. Savona-Baron, C. Riès, C. Chanseau, S. Bertrand, A. K. Mishra, E. Hindié, P. Fernandez and J. Schulz, Med Chem Commun., April 2016	Med Chem Commun.
		2014	Targeting neuropeptides receptors for cancer imaging and therapy: Perspectives with bombesin, neurotensin and neuropeptide-Y receptors. Morgat C, Mishra A.K, Varshney R, Allard M, Fernandez P, Hindié E. J Nucl Med. 2014;55(10)	J Nucl Med
		2014	A phantom-based method to standardize dose-calibrators for new β+ emitters: 68Ga as demonstrative working example. Morgat C, Mazère J, Fernandez P, Buj S, Vimont D, Schulz J, Lamare F. Nucl Med Commun. 2014.	Nucl Med Commun

Research achievements

publications published over the 2011-2016 period :

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP4 - Tracers and contrast agents	SUPSIFLU	2016	Gold-catalysed cross-coupling between aryldiazonium salts and arylboronic acids: probing the usefulness of photoredox conditions, Thomas Cornilleau, Philippe Hermange and Eric Fouquet, Chem Communication, July 2016	Chem Communication
	TARGLIN	2016	In Vivo Follow-up of Brain Tumor Growth via Bioluminescence Imaging and Fluorescence Tomography, Genevois C, Loiseau H and Couillaud F, International Journal of Molecular Sciences, Oct 2016	International Journal of Molecular Sciences
WP5 - Biological bioimaging markers	BIOPSYPROS-TAPROBE	2016	In vivo imaging of prostate cancer using an anti-PSMA scFv fragment as a probe, Mazzocco C, Fracasso G, Germain-Genevois C, Dugot-Senant N, Figini M, Colombatti M, Grenier N & Couillaud F, Scientific Reports 6, 23314, Mar 2016	Scientific report
	DIMI	2013	Neuroinflammatory imaging biomarkers : Relevance to Multiple Sclerosis and its therapy. Thomas Tourdias and Vincent Dousset. Neurotherapeutics. 2013 Jan; 10(1): 111–123.	Neurotherapeutics
	GMCOG	2016	Selective dentate gyrus disruption causes memory impairment at the early stage of experimental multiple sclerosis. V. Planche, A. Panatier, B. Hiba, E. Ducourneau, G. Raffard, N. Dubourdieu, M. Maitre, T. Lesté-Lasserre, B. Brochet, V. Dousset, A. Desmedt, S.H. Oliet, T. Tourdias. Brain Behavior and Immunity, dec 2016	Brain, Behavior, and Immunity
		2016	In Vivo 7T MR Quantitative Susceptibility Mapping Reveals Opposite Susceptibility Contrast between Cortical and White Matter Lesions in Multiple Sclerosis. X W. Bian, X E. Tranvinh, X T. Tourdias, X M. Han, X T. Liu, X Y. Wang, X B. Rutt, and X M.M. Zeineh, AJNR, oct 2016	AJNR Am J Neuroradiol
	IBIONI	2016	Early Fiber Number Ratio Is a Surrogate of Corticospinal Tract Integrity and Predicts Motor Recovery After Stroke, Antoine Bigourdan, MD*; Fanny Munsch, PhD*; Pierrick Coupé, PhD; Charles R.G. Guttmann, MD; Sharmila Sagnier, MD; Pauline Renou, MD; Sabrina Debruxelles, MD; Mathilde Poli, MD; Vincent Dousset, MD, PhD; Igor Sibon, MD, PhD; Thomas Tourdias, MD, PhD, Stroke, March 2016	Stroke
		2016	Cervical spinal cord DTI is improved by reduced-FOV with specific balance between numbers of diffusion gradient directions and numbers of averages; A Crombé, N Alberti, B Hiba, V Dousset, T Tourdias, AJNR, May 2016	AJNR Am J Neuroradiol
		2016	Hippocampal microstructural damage and memory impairment in clinically isolated syndrome, Planche V at al., MS journal., oct 2016	MS journal
		2015	Stroke location is an independent predictor of cognitive outcome, F. Munsch*; S. Sagnier MD*; J. Asselineau PhD; A. Bigourdan MD; C.R. Guttmann MD; S. Debruxelles MD; M. Poli MD; P. Renou MD; P. Perez MD PhD; V. Dousset MD PhD; I Sibon MD PhD*; Thomas Tourdias MD PhD*. Stroke, nov 2015	Stroke
		2014	Information processing speed impairment and cerebellar dysfunction in relapsing-remitting multiple sclerosis. . Ruet A, Hamel D, Deloire MS, Charré-Morin J, Saubusse A, Brochet B. J Neurol Sci. 2014 Oct 12;347(1-2):246-250	J Neurol Sci
	INNES	2016	Evaluation of a high-resolution micro-sized magic angle spinning (HRmMAS) probe for NMR-based metabolomic studies of nanoliter samples, Nghia Tuan Duong, Yuki Endo, Takahiro Nemoto, Hiroshi Kato, Anne-Karine Bouzier-Sore, Yusuke Nishiyamaab and Alan Wong, Analytical Method, Aug 2016	Analystical method
		2015	High-resolution NMR-based metabolic detection of microgram biopsies using a 1-mm HRμMAS prototype probe. Analyst, accepted 2015, Yusuke Nishiyama, Yuki Endo, Takahiro Nemoto, Anne-Karine Bouzier-Sore and Alan Wong.	Analyst

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP5 - Biological bioimaging markers	INNES	2015	High-resolution NMR-based metabolic detection of microgram biopsies using a 1-mm HRμMAS prototype probe. Analyst, accepted 2015, Yusuke Nishiyama, Yuki Endo, Takahiro Nemoto, Anne-Karine Bouzier-Sore and Alan Wong.	Analyst
		2015	Rapid adaptation of rat brain and liver metabolism to a ketogenic diet: an integrated study using 1H- and 13C-NMR spectroscopy. Maggie Roy, Marie-Christine Beauvieux,Jérôme Naulin, Dounia El Hamrani, Jean-Louis Gallis, Stephen C Cunnane and Anne-Karine Bouzier-Sore, Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism, Mars 2015	J Cereb Blood Flow Metab
		2015	Uncertainties in pentose-phosphate pathway flux assessment underestimate its contribution to neuronal glucose consumption: relevance for neurodegeneration and aging, Anne-Karine Bouzier-Sore and Juan P. Bolaños, Front Aging Neurosci. 2015; 7: 89.	Frontiers in Aging Neuroscience
		2013	13C-NMR spectroscopy applications to brain energy metabolism, Tiago B. Rodrigues, Julien Valette and Anne-Karine Bouzier-Sore. Frontiers in Neuroenergetics, déc 2013.	Front Neuroenergetics
		2013	Glucose and lactate metabolism in the awake and stimulated rat: a (13) C-NMR study. Sampol, D., Ostrofet, E., Jobin, M. L., Raffard, G., Sanchez, S., Bouchaud, V., Franconi, J. M., Bonvento, G., and Bouzier-Sore, A. K. Front Neuroenergetics 5, 5 (2013)	Front Neuroenergetics
	MIMATHUMAB	2016	A Recombinant Human Anti–platelet scFv Antibody Produced in Pichia pastoris for Atheroma Targeting. Amelie Vallet–Courbin, Mélusine Larivière, Agnès Hocquellet, Audrey Hemadou, Sarjapura–Nagaraja Parimala, Jeanny Laroche–Traineau, Xavier Santarelli, Gisèle Clofent–Sanchez, Marie–Josée Jacobin–Valat and Abdelmajid Noubhani. PLoS ONE, dec 2016	Plos One
		2016	Solid Lipid Nanoparticles for Image-Guided Therapy of Atherosclerosis, Khalid Oumzil, Michael A. Ramin, Cyril Lorenzato, Audrey Hémadou, Jeanny Laroche, Marie Josée Jacobin-Valat, Stephane Mornet, Claude-Eric Roy, Tina Kauss, Karen Gaudin, Gisèle Clofent-Sanchez, and Philippe Barthélémy, Bioconjugate Chemistry, jan 2016	Bioconjugate Chemistry
		2014	Nanoparticles functionalised with an anti-platelet human antibody for in vivo detection of atherosclerotic plaque by Magnetic Resonance Imaging. M.J Jacobin-Valat, J. Laroche-Traineau, M. Larivière, S. Mornet, S. Sanchez, M. Biran, C. Lebaron, J. Boudon, S. Lacomme, M. Cérutti, G. Clofent-Sanchez. Nanomedicine: Nanotechnology, Biology, and Medicine, 2014	Nanomedicine
	SCICOG & REACTIV	2016	Cerebellar assessment in early MS, Moroso A et al., Cerebellum journal, oct 2016	Cerebellum journal
		2016	Posterior lobules of the cerebellum and information processing speed at various stages of multiple sclerosis, Moroso A et al., JNNP journal, oct 2016	JNNP journal
		2015	Cognitive evaluation by tasks in a virtual reality environment in multiple sclerosis; D Lamargue-Hamel D, Deloire M, Saubusse A, Ruet A, Taillard J, Philip P, Brochet B. Paper in press in J Neurol Sci	J Neurol Sci
		2015	Deciphering depressive mood in relapsing-remitting and progressive multiple sclerosis and its consequences on quality of life. Delphine Lamargue Hamel, Mathilde Deloire, Aurélie Ruet, Julie Charré-Morin, Aurore Saubusse, Jean-Christophe Ouallet, Bruno Brochet. Paper in press in PLOS ONE	PLoS One

Research achievements

publications published over the 2011-2016 period :

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP5 - Biological bioimaging markers	TBI	2016	Improved long-term outcome after transient cerebral ischemia in aquaporin-4 knockout mice, Lorenz Hirt*, Andrew M Fukuda*, Kamalakar Ambadipudi,Faisil Rashid, Devin Binder, Alan Verkman, Stephen Ashwal,Andre Obenaus and Jerome Badaut, JCBFM, janvier 2016	Journal of Cerebral Blood Flow & Metabolism
		2016	Chronic cerebrovascular dysfunction after traumatic brain injury. Jullienne A, Obenaus A, Ichkova A, Savona-Baron C, Pearce WJ, Badaut J. J Neurosci Res. Jul 2016	J Neurosci Research
	TRANSFEAR	2016	4-Hz oscillations synchronize prefrontal–amygdala circuits during fear behavior, Nikolaos Karalis, Cyril Dejean, Fabrice Chaudun, Suzana Khoder, Robert R Rozeske, Hélène Wurtz, Sophie Bagur, Karim Benchenane, Anton Sirota, Julien Courtin & Cyril Herry, Nature Neurosciences, Feb 2016	Nature Neurosciences
		2016	Preventing long-lasting fear recovery using bilateral alternating sensory stimulation: a translational study, Wurtz, El-Khoury-Malhame, Wilhelm, Michael, Beetz, Roques, Reynaud, Courtin, Khalfa, Herry, Neuroscience, May 2016	Neurosciences
		2015	Neuronal Circuits for Fear Expression and Recovery: Recent Advances and Potential Therapeutic Strategies. C. Dejean, J. Courtin, R. Rozeske, M. C. Bonnet, V. Dousset, T. Michelet, and C. Herry. Biological Psychiatry Sep, 2015; 78:298–306	Biological Psychiatry
	PUBLICATION FROM THE COMMUNITY	2016	Radiologic imaging of the renal parenchyma structure and function, Nicolas Grenier, Pierre Merville and Christian Combe, Nature Reviews Nephrology, April 2016	Nature Reviews Nephrology
		2015	Multiple sclerosis lesions are better detected with 3D T1 gradient echo than with 2D T1 spin echo gadolinium enhanced imaging at 3 Tesla. Crombe A, Saranathan M, Ruet A, Durieux M, Roquefeuil E, Ouallet JC, Brochet B, Dousset V, Tourdias T. AJNR Am J Neuroradiol 2015 Mar;36(3):501-7.	AJNR Am J Neuroradiol
		2014	Optimization of white matter nulled magnetization prepared rapid gradient echo (MP-RAGE) imaging. Saranathan M, Tourdias T, Bayram E, Ghanouni P, Rutt BK. Magn Reson Med 2014 May 29.	Magn Reson Med
		2014	Optimization of Magnetization-Prepared 3-Dimensional Fluid Attenuated Inversion Recovery Imaging for Lesion Detection at 7 T. Saranathan M, Tourdias T, Kerr AB, Berstein JD, Kerchner GA, Han MH, Rutt BK. Investigative Radiology 2014 May 49(5):290-8.	Investigative Radiology
		2014	Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. Tourdias T, Saranathan M, Levesque IR, Su J, Rutt BK. Neuroimage, 2014 Jan 1;84:534-45.	Neuroimage
WP6 - Mathematical simulation and modeling	MOD	2016	Computational Trials: Unraveling Motility Phenotypes, Progression Patterns, and Treatment Options for Glioblastoma Multiforme, Fabio Raman, Elizabeth Scribner, Olivier Saut, Cornelia Wenger, Thierry Colin, Hassan M. Fathallah-Shaykh*, PlosOne, jan 2016	PLoS One
		2016	Spatial Modeling of Tumor Drug Resistance : the case of GIST Liver Metastase, Lefebvre G., Cornelis F., Cumsille P., Colin T., Poignard C., Saut O. Mathematical Medicine & Biology, March 2016	Mathematical Medicine & Biology
		2015	Patient-specific simulation of tumor growth, response to the treatment, and relapse of a lung metastasis: a clinical case. Thierry Colin, François Cornelis, Julien Jouganous, Jean Palussière and Olivier Saut, Jouganous et al. Journal of Computational Surgery (2015) 2:1	Journal of Computational Surgery
		2015	Computational Modelling of Metastasis Development in Renal Cell Carcinoma, Etienne Baratchart, Sébastien Benzekry*, Andreas Bikfalvi*, Thierry Colin*, Lindsay S. Cooley, Raphäel Pineau, Emeline Ribot, Olivier Saut, Wilfried Souleyreau, PlosOne Nov 2015	PLoS One

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP7 - Cohort Imaging Methodology	ACTE	2015	Neuroimaging and Alcoholism. Chanraud S, Bernard C. Annales Médico-Psychologiques 2015	Annales Médico-Psychologiques
		2014	Compensatory recruitment of neural resources in chronic alcoholism. Chanraud S. and Sullivan EV. Handbook of Clinical Neurology, Vol. 125, 2014	Handbook of Clinical Neurology
	ADPP	2016	Age-Related Modifications of Diffusion Tensor Imaging Parameters and White Matter Hyperintensities as Inter-Dependent Processes, Amandine Pelletier*, Olivier Periot, Bixente Dilharreguy, Bassem Hiba, Martine Bordessoules, Sandra Chanraud, Karine Pérès, Hélène Amieva, Jean-François Dartigues, Michèle Allard and Gwénaëlle Catheline, Frontiers in Aging Neurosciences, jan 2016	Frontiers in Aging Neuroscience
		2016	Activity/rest cycle and disturbances of structural backbone of cerebral networks in aging, Marion Baillet, Bixente Dilharreguy, Karine Pérès, Jean-François Dartigues, Willy Mayo, Gwenaëlle Catheline, Neuroimage, Sept 2016	Neuroimage
	COBRASCAN	2016	Lung morphology assessment of cystic fibrosis using MRI with ultra-short echo time at submillimeter spatial resolution, Gaël Dournes & Fanny Menut & Julie Macey & Michaël Fayon & Jean-François Chateil & Marjorie Salel & Olivier Corneloup & Michel Montaudon & Patrick Berger & François Laurent, Eur Radiol, feb 2016	European Radiology
		2016	Quiet Submillimeter MR Imaging of the Lung Is Feasible with a PETRA Sequence at 1.5 T1, Gaël Dournes, MD, PhD, David Grodzki, PhD, Julie Macey, MD, Pierre-Olivier Girodet, MD, PhD, Michaël Fayon, MD, PhD, Jean-François Chateil, MD, PhD, Michel Montaudon, MD, PhD, Patrick Berger, MD, PhD, François Laurent, MD, Radiology, july 2015	Radiology
		2016	CT evaluation of small pulmonary vessels area in patients with COPD with severe pulmonary hypertension, Florence Coste, Gaël Dournes, Claire Dromer, Elodie Blanchard, Véronique Freund-Michel, Pierre-Olivier Girodet, Michel Montaudon, Fabien Baldacci, François Picard, Roger Marthan, Patrick Berger, François Laurent, Thorax, april 2016	Thorax

b) 12 TRAIL publications belong to the 10% of most quoted publications in the world over the 2011-2015 period (26% of publications of that period):

PUBLICATIONS	AUTHORS	JOURNAL	YEAR	QUOTES	RESEARCH PROJECT	WP
Collaborative patch-based super-resolution for diffusion-weighted images	Coupé, P., Manjón, J.V., Chamberland, M., Descoteaux, M., Hiba, B.	NeuroImage	2013	20	HRDTI	2
Diffusion Weighted Image Denoising Using Overcomplete Local PCA	Manjón, J.V., Coupé, P., Concha, L., Buades, A., Collins, D.L., Robles, M.	PLoS ONE	2013	20	HRDTI	2
Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T	Tourdias, T., Saranathan, M., Levesque, I.R., Su, J., Rutt, B.K.	NeuroImage	2014	19	PUBLICATION FROM THE COMMUNITY	5
Targeting neuropeptide receptors for cancer imaging and therapy: Perspectives with bombesin, neurotensin, and neuropeptide-Y receptors	Morgat, C., Mishra, A.K., Varshney, R., Allard, M., Fernandez, P., Hindié, E.	Journal of Nuclear Medicine	2014	17	PRITOR	4

Research achievements

PUBLICATIONS	AUTHORS	JOURNAL	YEAR	QUOTES	RESEARCH PROJECT	WP
Optimized patchMatch for near real time and accurate label fusion.	Ta, V.T., Giraud, R., Collins, D.L., Coupé, P.	Medical image computing and computer-assisted intervention	2014	14	HRDTI	2
Glucose and lactate metabolism in the awake and stimulated rat: a (13) C-NMR study	Sampol, D., Ostrofet, E., Jobin, M.-L., Raffard, G., Sanchez, S., Bouchaud, V., Franconi, J.-M., Bonvento, G., Bouzier-Sore, A.	Frontiers in Neuroenergetics	2013	14	INNES	5
Rotation-invariant multi-contrast non-local means for MS lesion segmentation	Guizard, N., Coupé, P., Fonov, V.S., Manjón, J.V., Arnold, D.L., Collins, D.L.	NeuroImage: Clinical	2015	14	HRDTI	2
Quiet submillimeter MR imaging of the lung is feasible with a PETRA sequence at 1.5 T	Dournes, G., Grodzki, D., Macey, J., Girodet, P.-O., Fayon, M., Chateil, J.-F., Montaudon, M., Berger, P., Laurent, F.	Radiology	2015	13	COBRAS-CAN	7
MRI noise estimation and denoising using non-local PCA	Manjón, J.V., Coupé, P., Buades, A.	Medical Image Analysis	2015	13	HRDTI	2
Neuronal Circuits for Fear Expression and Recovery: Recent Advances and Potential Therapeutic Strategies	Dejean, C., Courtin, J., Rozeske, R.R., Bonnet, M.C., Dousset, V., Michelet, T., Herry, C.	Biological Psychiatry	2015	13	TRANSFEAR	5
Nanoparticles functionalised with an anti-platelet human antibody for in vivo detection of atherosclerotic plaque by magnetic resonance imaging	Jacobin-Valat, M.-J., Laroche-Traineau, J., Larivière, M., Mornet, S., Sanchez, S., Biran, M., Lebaron, C., Boudon, J., Lacomme, S., Cérutti, M., Clofent-Sanchez, G.	Nanomedicine: Nanotechnology, Biology, and Medicine	2015	6	MIMATHU-MAB	5
Uncertainties in pentose-phosphate pathway flux assessment underestimate its contribution to neuronal glucose consumption: Relevance for neurodegeneration and aging	Bouzier-Sore, A.-K., Bolaños, J.P.	Frontiers in Aging Neuroscience	2015	6	INNES	5

B.32 Scientific communication during international event

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	HIFU	Oxford University	Alteration of the blood brain barrier induced by HIFU	2013	Oxford	UK
		Leloir Institute	Alteration of the blood brain barrier induced by HIFU	2013	Buenos Aires	Argentina
		23rd Congress Shangai	Alteration of the blood brain barrier induced by HIFU	2013	Shangai	China
	MRGHIFU	ISTU 2016	Bour P, Marquet F, Ozenne V, Toupin S, Dumont E, Quesson B. Simultaneous monitoring of MR-ARFI and MR-thermometry during HIFU ablation. ISTU 2016, Tel-Aviv, Israel.	2016	Tel-Aviv	Israel

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	MRGHIFU	ISMRM 2016	Bour P, Marquet F, Vaillant F, Ozenne V, Toupin S, Lepetit-coiffe M, Dumont E, Quesson B. Non-Invasive Cardiac Stimulation with MR Guided HIFU: A Rapid, Cardiac Triggered, MR-ARFI Method for Direct Visualization of Stimulation Site and Assessment of Tissue Stiffness.	2016	Singapour	Singapour
		COST radiomag meeting	Couillaud F. Hyperthermia of tumor microenvironment for therapeutic purposes. (2016), April 7-9.	2016	Athens	Greece
		COST radiomag meeting	Couillaud F. Odyssey of nanoparticles from the tube to the tumor cells. How to bring bricks together? (2016), April 21-22.	2016	London	UK
		5th international focused ultrasound symposium	Marquet F, Bour P, Vaillant F, Amraoui S, Dubois R, Ritter P, Haïssaguerre M, Hocini M, Bernus O, Quesson B. Ex vivo and in vivo non-invasive ultrasound-based cardiac pacing.	2016	Washington	USA
		ISTU 2016	Marquet F, Bour P, Vaillant F, Amraoui S, Dubois R, Ritter P, Haïssaguerre M, Hocini M, Bernus O, Quesson B. Non-invasive cardiac pacing using images-guided focused ultrasound ex vivo and in vivo in pigs.	2016	Tel-Aviv	Israel
		37th Heart rhythm Society (HRS)	Marquet F, Bour P, Vaillant V, Amraoui S, Dubois R, Ritter P, Haissaguerre M, Hocini M, Bernus O, Quesson B. In vivo non-invasive ultrasound-based cardiac pacing in pigs.	2016	San Francisco	USA
		11th Interventional MRI Symposium	Ozenne V, Toupin S, Bour P, Denis de Senneville B, Vaussy A, Lepetit-Coiffé M, Jaïs P, Cochet H, Quesson B. First Clinical Evaluation of Real-Time Cardiac MR Thermometry.	2016	Baltimore	USA
		ISMRM 2016	Ozenne V, Troadec T, Bour Pierre, Toupin S, Dumont E, Quesson B. Automatic Temperature Control During MR Guided Catheter Based Radiofrequency Ablation of the Heart.	2016	Singapour	Singapour
		ISMRM 2016	OzenneV, Toupin S, Bour P, Denis de Senneville B, Vaussy A, Lepetit-Coiffé M, Jaïs P, Cochet H, Quesson B. First Clinical Evaluation of Real-Time Cardiac MR Thermometry.	2016	Singapour	Singapour
		11th Interventional MRI Symposium	Toupin S, Bour P, Ozenne V, Lepetit-Coiffé M, Denis de Senneville B, Schneider R, Chaumeil A, Jais P and Quesson B. In Vivo monitoring of cardiac radiofrequency ablation by real-time MR Thermometry.	2016	Baltimore	USA
		ISMRM 2016	Toupin S, Lepetit-Coiffe M, Bour P, Ozenne V, denis de Senneville B, Schneider R, Jenkins K, Chaumeil A, Jais P, Quesson B. In-Vivo Echo-Navigated MR Thermometry for Real-Time Monitoring of Cardiac Radiofrequency Ablation. Summa cum laude award	2016	Singapour	Singapour
		37th Heart rhythm Society (HRS)	Toupin S, Lepetit-Coiffé M, Bour P, Ozenne V, Denis de Senneville B, Schneider R, K Jenkins, Chaumeil A, Jais P, Quesson B. Real-time visualization of temperature distribution in the myocardium during adiofrequency ablation by Magnetic Resonance thermometry.	2016	San Francisco	USA
		11th Interventional MRI Symposium	Toupin S, Ozenne V, Bour P, Lepetit-Coiffé M, Denis de Senneville B, Schneider R, Chaumeil A, Jais P, Quesson B. Online visualization of lesion extent during RF ablation by thermal dose mapping: correlation with post-ablation T1-w imaging and gross-pathology.	2016	Baltimore	USA

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	MRGHIFU	ISTU 2016	Bour P, Marquet F, Ozenne V, Toupin S, Dumont E, Quesson B. Simultaneous monitoring of MR-ARFI and MR-thermometry during HIFU ablation. ISTU 2016, Tel-Aviv, Israel.	2016	Tel-Aviv	Israel
		Congrès international ISMRM	Bour P, Marquet F, Toupin S, Lepetit-Coiffé M, Quesson B. Fast Simultaneous Temperature and Displacement Imaging During HIFU Ablation in Swine Liver.	2015	Toronto	Canada
		Congrès internatio-nal HRS	Marquet F, Bour P, Vaillant F, Amraoui S, Dubois R, Ritter P, Haïssaguerre M, Hocini M, Bernus O, Quesson B. Contactless cardiac stimulation with MRI guided High Intensity Focused Ultrasound.	2015	Boston	USA
		Congrès international ESMRMB	Toupin S, Ozenne V, Bour P, Quesson B, De Senneville BD. A robust PCA-based motion estimation approach for MR Ther-mometry radiofrequency ablation monitoring.	2015	Edinburg	UK
		IEEE International Ultrasonics Symposium	Marquet F, Bour P, Amraoui S, Vaillant F, Dubois R, Quesson B. Non-invasive cardiac stimulation by MRI-guided focused ultrasound: a feasibility study on isolated beating pig heart. IEEE International Ultrasonics Symposium Chicago USA	2014	Chicago	USA
2	HRDTI	20th annual mee-ting of Human Brain Mapping	Impact of DWI denoising on Track-Density Imaging. Coupe P, Periot O, Manjon J, Hiba B, Allard5 M. 20th annual meeting of Human Brain Mapping 2014, Hamburg, Germany	2014	Hamburg	Germany
	NEWFISP	ISMRM2016	3D Longitudinal MRI Studies on Novel Tissue-Engineered Bone Constructs in Living Rats : Volume & Perfusion Assess-ments	2016	Singapour	Singapour
		ISMRM2016	4D Flow MRI of the Cardiovascular System in Small Animals at 7T with an Ultrashort TE Sequence Combined with an In-jection of Iron Nanoparticle	2016	Singapour	Singapour
		ESMI	T1 Longitudinal quantification of iron-oxyde particles using a 3D UTE Spiral Look-Locker sequence at 7T	2016	Utrecht	Nether-lands
		ISMRM 2015	5 communications Posters ou orales	2015	Toronto	Canada
3	ONCOFLUX	ISMRM2016	A combined microcoil and microdialysis approach to measure metabolic response in real-time.	2016	Singapour	Singapour
		ISMRM2016	Simultaneous imaging and 1H spectroscopy of small volume (1 µl) intracerebral microdialysate in healthy and glioblasto-ma-bearing rats using highly sensitive micro-coils.	2016	Singapour	Singapour
		European Molecular Imaging Meeting. Utrecht	Simultaneous MRI and MRS spectrocopy of small volume (1 microlitre) intracerebral metabolites: a combined microdialy-sis and microcoil application	2016	Utrecht	Nether-lands
		ISMRM meeting	MR Spectroscopy of very small volumes (< 0.4 µl) of 13C-la-belled metabolites using microcoil detection: application to online measurements of cerebral microdialysate, ISMRM 2015	2015	Toronto	Canada
		EUROMAR meeting	Online monitoring of brain metabolites: A microdialysis and microcoil approach, CMR meeting	2015	Prague	Czech Republic
		ISMRM	MR Spectroscopy of very small volumes (< 0.4 µl) of 13C-la-belled metabolites using microcoil detection: application to online measurements of cerebral microdialysate	2014	Toronto	Canada

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
3	TRAILDNP	Asia-Pacific EPR Symposium	Elodie Parzy (oral communication), In vivo Mapping of Protease Activity using Overhauser-enhanced MRI: Challenges and Promises	2016	Irkurtsk	Russia
		ISMRM Merit AWARD ISMRM 2015 30 May - 05 June 2015	Resonance frequency-shifting nitroxide for probing proteolytic activity in vivo using the Overhauser-enhanced MRI technique Neha KOONJOO, Gérard Audran, Lionel Bosco, Paul Brémond, Elodie Parzy, Philippe Massot, Matthieu Lepetit-Coiffé, Jean-Michel Franconi, Sylvain R.A Marque, Eric Thiaudière, and Philippe Mellet	2015	Toronto	Canada
		ENIM	In vivo OMRI of proteolysis. ENIM 2014 Antwerp Belgium	2014	Antwerp	Belgium
		ISMRM	In vivo OMRI of proteolysis. ISMRM 2014 Milano Italy	2014	Milano	Italy
4	IMMELAPT	COST Thematic Workshop "Bio-inspired Nanotechnologies for Biosensing"	APTAMERS, CLEVER OLIGONUCLEOTIDES FOR BIO-SENSING	2013	Sitges	Spain
		Tohoku University	International Symposium, Tohoku University, Sendai, Japan	2013	Sendai	Japan
		NanobioEurope	NanobioEurope	2013	Toulouse	France
	INNES	EWCBR 2016	Lactate: more than a neuronal energetic subtrate. par Bouzier–Sore A. K. (conférencier invité)	2016	Villars sur-Ollon	Switzerland
		ESMRMB 2016	Short term effect of lactate neuroprotection in neonate hypoxia–ischemia: a metabolic or signal effect? par Mazuel, L., S. Sanchez, J.–F. Chateil, and A.K. Bouzier–Sore (communication orale)	2016	Vienna	Austria
		ESMRMB 2016	Trans–resveratrol supplementation during gestation and lactation attenuates hypoxia–ischemia brain lesions in rat neonates par Mazuel, L., U. Dumont, S. Sanchez, J. Blanc, V. Bouchaud, J.F. Chateil, M.–C. Beauvieux, and A.K. Bouzier–Sore (poster)	2016	Vienna	Austria
	NEPMIP	Euskampus 26-27/11/15	Formulation of nanoobjects for Magnetic Particles Imaging	2015	San Sebastian	Spain
	PRITOR	Annual Meeting of the European Association of Nuclear Medicine 2016	Champion C, Morgat C, Quinto MA, Zanotti-Fregonara P, Hindié E. Monte-Carlo comparison of four beta-emitting radionuclides of interest for targeted radionuclide therapy of small tumors: 177Lu, 67Cu, 47Sc and 161Tb.	2016	Barcelone	Spain
		Annuel Meeting of the Endocrine Society 2016	Velayoudom-Céphise FL, Morgat C, Schwartz P, Nunès ML, Guyot M, Schulz J, Mazère J, Gaye D, Smith D, Hindié E, Fernandez P, Tabarin A. Detection of duodenal and pancreatic neuroendocrine tumors in MEN1 patients: comparison of the performances of 68Ga-DOTA-TOC PET/CT and 111In-pentetreotide	2016	Boston	USA
		Theranostics world congress Ga-68 and PRRT	Development of a 68Ga-ranatensin analog for bombesin receptor PET molecular imaging (communication orale)	2015	Baltimore	USA
		Congress of the European Association of Nuclear Medicine	Terbium-161 a promising radionuclide for the irradiation of tumor cells and micrometastases: Monte Carlo assessment using CELLDOSE (communication orale)	2015	Hamburg	Germany

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
4	PRITOR	Congress of the European Association of Nuclear Medicine	Champion C, Zanotti-Fregonara P, Quinto M. A, Morgat C, Hindié E. Comparative efficacy of 90Y, 177Lu and 111In for the irradiation of tumor cells and micrometasases: a Monte Carlo study using CELLDOSE.. 2014 Gotenburg (Sweden). Congress of the European Association of Nuclear Medicine (oral) Gotenburg Sweden.	2014	Gotenburg	Sweden
		Congress of the European Association of Nuclear Medicine	Morgat C, Mazère J, Fernandez P, Buj S, Vimont D, Schulz J, Lamare F. Methodological proposal to standardize dose-calibrators for new β+ emitters: 68Ga as demonstrative working example. 2014 Gotenburg (Sweden). Congress of the European Association of Nuclear Medicine (oral) Gotenburg Sweden.	2014	Gotenburg	Sweden
		Congress of the European Association of Nuclear Medicine	Morgat C, Varshney R, Schulz J, Savona-Baron C, Vimont D, Riès C, Bertrand S, Allard M, Mishra A.K, Fernandez P, Hindié E. Identification of GRPR in ER-positive breast cancer cells as molecular basis to develop a new 68Ga-GRPR-antagonist (68Ga-DOTA-RV_15) for PET molecular imaging.. 2014 Congress of the European Association of Nuclear Medicine (poster) Gotenburg Sweden.	2014	Gotenburg	Sweden
5	BIOPSY-PROSTA-PROBE	28th European Congress of Radiology	In vivo imaging of prostate cancer using an anti-PSMA fragment as a probe. Mazzocco C, Grenier N, Fracasso G, Germain-Genevois C, Dugot-Senant N, Couillaud F.	2016	Vienna	Autria
	GMCOG	International meeting on cognition in multiple sclerosis (IMSCOGS)	Cognitive impairment in primary progressive multiple sclerosis	2016	New-York	USA
		European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)	Early cerebellar cognitive profile in multiple sclerosis: From saccadic impairment to grey matter alterations	2016	London	UK
		European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)	Efficacy and safety of alemtuzumab in 104 patients with active relapsing-remitting MS: one-year follow-up in France	2016	London	UK
		International meeting on cognition in multiple sclerosis (IMSCOGS)	Hippocampal microstructural damage and memory impairment in multiple sclerosis: A translational study from animal models to CIS and MS patients	2016	New-York	USA
		10th annual meeting of the FENS	Membrane dynamics of AQP4: a new key pathway for physiopathological brain cell communication?	2016	Copenhagen	Danemark
	IBIONI	ECTRIMS	"Hippocampal microstructural damage and memory impairment in clinically isolated syndrome". V. Planche	2015	Barcelona	Spain
		ISMRM	"Imaging biomarker and pathophysiology of early memory impairment in multiple Sclerosis: a pre-clinical study with diffusion-tensor imaging of hippocampal layers". T. Tourdias	2015	Toronto	Canada
		ECTRIMS	"Vulnerability of dentate gyrus to microglial activation leads to early memory impairment in a model of multiple sclerosis." V. Planche	2015	Barcelona	Spain

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
5	IBIONI	ECTRIMS	CEREBELLAR SUB-STRUCTURES IN COGNITIVE IMPAIRMENT: Volumetric And Microstructural Analyses At Different Stages Of Multiple Sclerosis. A Moroso.	2015	Barcelona	Spain
		IMSCOGS	ECOLOGICAL ASSESSMENT IN COGNITIVE SCREENING in MS B Brochet IMSCOGS 2014 Barcelona Spain	2014	Barcelona	Spain
		ECTRIMS ACTRIMS	INCLUDING ECOLOGICAL ASSESSMENT IN COGNITIVE SCREENING in MS D Hamel ECTRIMS ACTRIMS 2014 Boston USA	2014	Boston	USA
	INNES	Gordon Conference	Early neuroprotective effect of lactate in neonatal hypoxic ischemic brain damages.	2015	Ventura, CA	USA
		ESMRMB	Early neuroprotective effect of lactate in neonatal hypoxic ischemic brain damages.	2015	Edinburg	Ecosse
		ISMRM	MR Spectroscopy of very small volumes of 13C-labelled metabolites using microcoil detection: application to online measurements of cerebral microdialysate.	2015	Toronto	Canada
		Euroglia	Neonatal hypoxic ischemic brain damages: early neuroprotective effect of lactate.	2015	Bilbao	Espagne
		Conférence Université Lausanne	NMR spectroscopy « for dummies » and its application to decipher metabolism. Conférence invitée Lausanne Suisse	2014	Lausanne	Switzerland
		ISMRM	Towards MRS using High–Resolution Magic–Angle Coil Spinning: application to brain metabolism. ISMRM Milan Italie	2014	Milan	Italy
		Euroglia	Euroglia, Berlin, juillet 2013 : organisation d'un symposium « ASTROCYTE NETWORK CONTRIBUTION IN NEUROIMAGING SIGNALS » et conférence « Functional neuro-energetic and brain imaging: how do astrocytes contribute to the signal? »	2013	Berlin	Germany
		Gordon conférence	Gordon conference, Ventura, USA, mars 2013 : poster	2013	Ventura	USA
	MIMA-THUMAB	10th International Conference and Exhibition on Nanomedicine and Nanotechnology in Health Care	Targeted nanoparticles for multimodal molecular imaging in a mouse model of atherosclerosis (M Larivière)	2016	Bangkok	Thailande
		10th International Conference and Exhibition on Nanomedicine and Nanotechnology in Health Care	Theranostic of atherosclerosis using human antibody–targeted multi–modal nanoparticles for in situ drug delivery (G Clofent-Sanchez)	2016	Bangkok	Thailande
		7th PEGS Europe Protein & Antibody Engineering Summit	Theranostic of atherosclerosis: a high throughput method based on flow cytometry for the screening of phage-scFv (A Hémadou)	2016	Lisbonne	Portugal
		PEGS Europe Protein & Antibody Engineering Summit November 2015	A high-throughput method based on flow cytometry for the screening of phage-scFvs for the theranostic of atherosclerosis	2015	Lisbon	Portugal

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
5	MIMA-THUMAB	Euskampus 2015	Multi-modal nanoparticles for atherosclerosis imaging	2015	San Sebas-tien	Spain
		Conferences in the Baker Heart and Diabetes Institute, Février 2015	Theranostic of atherosclerosis using human antibody-targe-ted multi-modal nanoparticles for in situ delivery of drugs	2015	Melbourne	Autralia
		10th International Conference on the Scientific and Clini-cal Applications of Magnetic Carrier	10th International Conference on the Scientific and Clini-cal Applications of Magnetic Carriers, Dresden, Germany (10-14 juin 2014); Versatile and Multimodal Imaging Tool for Biological Applications;Adumeau L., Laroche-Traineau J., Jacobin Valat M.-J., Nouhbani M., Clofent-Sanchez G., Duguet E., Mornet S.	2014	Dresden	Germany
	TBI	Gordon Research Conference	«CNS Barrier Function in Juvenile Traumatic Brain Injury»	2016	New Lon-don, NH	USA
6	NEKOMRI	ESTI 2015	Lung morphology assessment of cystic fibrosis using MRI with ultrashort echo time at submillimeter spatial resolution	2015	Barcelone	Espagne
		RSNA 2015	Lung morphology assessment of cystic fibrosis using non-contrast enhanced proton MRI with submillimeter details at 1.5 Tesla	2015	Chicago	États-Unis
		CAIP 2015	Precise cross-section estimation on tubular organs	2015	Valetta	Malte
7	ACTE	Human Brain Map-ping	Age-related differences in time course of brain activation and connectivity during associative learning.	2016	Genève	Suisse
		Cognitive Neu-roscience Society Congress	Age-related differences in time course of brain activation and connectivity during feedback-based associative learning.	2016	San Francisco	USA
		EFIC 8th Internatio-nal Pain in Europe Congress	«Brain functional connectivity and morphology changes in medication-overuse headache: evidence for addiction-related processes.» Radat F., Di Scala G ., Dilharreguy B., Schoenen J., Allard M., Chanraud S. Octibre 2013	2015	Firenze	Italy
		Donders Discus-sions.	«Motor control in aging: Sensori-motor network connectivity at rest and motor performance» - Dupuy M. Novembre 2015	2015	Nijmegen	The Nether-lands
	COBRAS-CAN	European Society of Thoracic Imaging	G. Dournes, F. Coste, C. Dromer, F. Baldacci, F. Picard, M. Mon-taudon, R. Marthan, P. Berger, F. Laurent. CT measurement of small vessels as a tool to phenotype COPD subjects with severe pulmonary hypertension. European Society of Thoracic Ima-ging, Amsterdam 2014	2014	Ams-terdam	The Nether-lands
	TRAIL & TACKS	23rd Annual Mee-ting of the Inter-national Society of Magnetic Reso-nance in Medicine (ISMRM)	Poster : Recognition of bundles in healthy and severely di-seased brains" by Garyfallidis E, Côté M-A, Hau J, Perchey G, Petit L, Cunnanne SC, Descoteaux M (2015)	2015	Toronto	Canada
		Conférence au La-boratoire d'Imagerie de la Connectivité de Sherbrooke (SCIL)	Hau J Mapping whole brain white matter tracts in 410 healthy humans. Conférence au Laboratoire d'Imagerie de la Connectivité de Sherbrooke (SCIL), Université de Sherbrooke, Sherbrooke Canada	2014	Sherbrooke	Canada

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
7	TRAIL & TACKS	Conférence au Brain Imaging and Analysis Center (BIAC)	Petit L (2014) Stem-based approach to study the anatomical connectivity of human brain white matter pathways. The inferior fronto-occipital fasciculus. Conférence au Brain Imaging and Analysis Center (BIAC), Duke University Medical Center Durham USA	2014	Durham	USA
		20th Conference of the Organization for Human Brain Mapping	Poster : Anatomical connectivity of the inferior fronto-occipital fasciculus using stem-based tractography. By Hau J, Perchey G, Sarubbo S, Joliot M, Crivello F, Jobard G, Zago L, Mellet E, Mazoyer B, Tzourio-Mazoyer N, Petit L. 20th Conference of the Organization for Human Brain Mapping Hambourg Allemagne	2014	Hamburg	Germany
		20th Conference of the Organization for Human Brain Mapping	Poster : Stem-based tractography to study the anatomical connectivity of human brain white matter pathways. By Hau J, Sarubbo S, Perchey G, Crivello F, Joliot M, Zago L, Jobard G, Mellet E, Mazoyer B, Tzourio-Mazoyer N, Petit L 20th Conference of the Organization for Human Brain Mapping Hambourg Allemagne	2014	Hamburg	Germany
		ISMRM Scientific Workshop	Hau J, Sarubbo S, Petit L (2013) Stem-based tractography of long association fibers of the human brain. In: ISMRM Scientific Workshop - Diffusion as a Probe of Neural Tissue Microstructure. Podstrana (Croatia).	2013	Podstrana	Croatia

Research achievements

B.4 Patents

CARDIOLOGY

"Antibodies for molecular imaging of vulnerable plaques in atherosclerosis."
Number and publication date : WO2013072438 - 23/05/2013.
Inventors : Gisèle Clofent-Sanchez, Kamel Deramchia, Marie-Josée Jacobin,Stéphane Bonetto, Jeanny Traineau.

"Method for fat quantification in a region of the heart."
Number and publication date : WO2015165978 - 05/11/2015.
Inventors : Hubert Cochet, Pierre Jaïs.
v
"Method to control a target area of the heart, ablation method of target area of the heart, associated system".
Number and publication date : WO2016034594- 10/03/2016.
Inventors : Fabrice Marquet, Pierre Bour, Bruno Quesson, Fanny Vaillant.

"Method to control focused ultrasound calibration for cardiac stimulation, cardiac stimulation method, associated systems and devices."
Number and publication date : WO2016034590- 10/03/2016.
Inventors : Fabrice Marquet, Pierre Bour, Bruno Quesson, Fanny Vaillant, Rémi Dubois.

"Lipid based nanocarrier compositions loaded with metal nanoparticles and therapeutic agent."
Number and publication date : WO2016170010 - 27/10/2016.
Inventors : Jean-Philippe Barthélémy, Khalid Oumzil, Gisèle Clofent-Sanchez, Marie-Josée Jacobin, Jeanny Laroche-Traineau, Stéphane Mornet, Karen Gaudin, Abdelmajid Noubhani, Xavier-François Santarelli.

NEUROLOGY

"Stroke prediction : methods and tools."
Number of deposit : PCT/FR2015/053480
Date of deposit : 14/12/2015
Inventors : Thomas Tourdias, Vincent Dousset, Igor Sibon, Fanny Munsch, Paul Perez, Julien Asselineau.

ONCOLOGY

"Matrix metalloproteinase 9 (MMP-9) aptamer and uses thereof."
Number and publication date :WO2013153138 - 17/10/2013.
Inventors : Jean-Jacques Toulmé, Sonia Da Rocha, Eric Dausse, Michèle Allard, Laurent Azéma.

"Kits-of-parts comprising Nucleic Acids able to form a kissing complex and their uses thereof."
Number and publication date : WO2015071385 - 21/05/2015.
Inventors : Jean-Jacques Toulmé, Eric Dausse, Guillaume Durand, Eric Peyrin, Corinne Ravelet.

"Method for tumor growth prediction".
Number and publication date : WO2016097050 - 23/06/2016.
Inventors : Thierry Colin, Olivier Saut, Marie Martin, Julie Jouganous, Julie Joie.

PNEUMOLOGY

"Method for MRI characterisation of airways lung."
Number of deposit : PJ2015-054/BV2016-007
Date of deposit : 05/2016
Inventors : Gaël Dournes, Fabien Baldacci, François Laurent, Patrick Berger.

C/ Scientific animation and training

C.1 Conferences

TRAIL teams invited 37 international speaker to give lectures in Bordeaux.

DATE	SPEAKER	ORGANIZATION	LECTURE
November 2012	Dr Pr Marco Essig	Heidelberg University	Anticipating medical imaging research evolutions
April 2013	Dr Ernesto SANZ-ARIGITA	CITA Alzheimer, San Sebastian	Multidimensional biomarkers for early detection of neurodegeneration
July 2013	Professor Jeff W.M. BULTE	The Johns Hopkins University School of Medicine Baltimore	Seeing Cells with MRI
	Professor Martin MEYER	Department of Psychology, Plasticity and Learning in the healthy aging brain, University of Zurich	Time, speech, and the right hemisphere
November 2013	Professor Yasutaka FUSHIMI	Department of Diagnostic Imaging and Nuclear Medicine – Kyoto University	Cooperation between Kyoto University and Toshiba Medical
September 2013	Dr Wafaa ZARAOUI	University of Marseille	Brain sodium MRI: implications for multiple sclerosis
	Dr Franz SCHMITT	Siemens Research and Developement	Most recent development of High performance gradients and Ultra High Field
	Dr Lori BRIDAL	University Pierre et Marie Curie	Evaluating tumor vascular structure and its response to therapy with pre-clinical contrast-enhanced ultrasound
	Pr Mike MODO	University of Pittsburgh	Image-guided injection and non-invasive monitoring of tissue engineering in stroke
	Pr Constantin COUSSIOS	BUBBL, Oxford University	Real-time passive acoustic mapping of tissue ablation and drug delivery by ultrasound
	Pr Sébastien LECOMMANDOUX	University of Bordeaux	Biomimetic polymersomes, a promising platform towards personalized nanomedicine
January 2014	Pr Dennis PARKER	Utah Center for Advanced Imaging Research, Salt Lake City	MRI Guided Focused Ultrasound of the Breast
May 2014	Pr Brian RUTT	Stanford School of Medicine	Neuroimaging at ultra high field
	Aurobrata GHOSH	Inria Sophia-Antipolis, France	Diffusion MRI: From Diffusion to Brain connectomics
July 2014	Dr Christopher HAGEMEYER	Vascular Biotechnology Laboratory at Baker IDI in Melbourne	Enzyme-mediated Site-specific Bioconjugation for Molecular Imaging and Drug Delivery
September 2014	Pr David PERRIN	Department of Chemistry, University of British Columbia, Vancouver, CANADA	One-step Kit-like Radiofluorination of Peptides and other large molecules

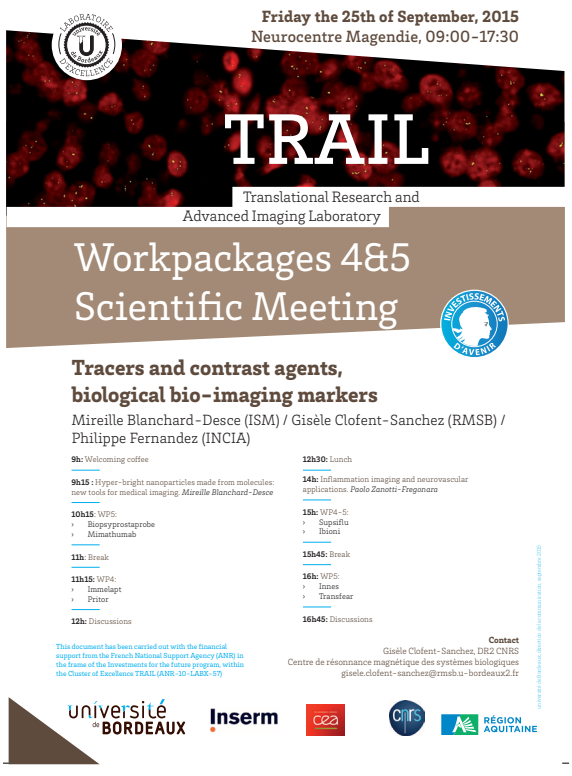
Scientific animation and training

DATE	SPEAKER	ORGANIZATION	LECTURE
January 2015	Dr. Nicoleta BAXAN	Bruker BioSpin MRI GmbH, Ettlingen, Germany	Magnetic Particle Imaging: A Novel Fast 3D In Vivo Imaging Modality based on Magnetic Nanoparticle Contrast Agents
February 2015	Pr Juan P. BOLANOS	Salamanque University	Molecular bases of the metabolic programs of neurons and astrocytes
April 2015	Pr Juan P. BOLANOS	Salamanque University	Astrocytes boost neuronal protection during glutamatergic neurotransmission
May 2015	Pr Yukio MIKI	Osaka City University	Imaging of the pituary
	Pr Juan P. BOLANOS	Salamanque University	Mitochondrial respiratory chain assembly dictates differential ROS production in neurons and astrocytes
July 2015	Dr Stanislas RAPACCHI	University of California, Los Angeles	Accélération de l'Angiographie par IRM par Compressed Sensing
	Dr Karen ALT	Baker Heart and Diabetes Institute, Vascular Biotechnology Laboratory, Melbourne, Australia	Platelets : good or bad guys
September 2015	Prof. Shuh NARUMIYA	Kyoto University	Aneurysm and inflammation
	Dr Robert INNIS	NIH, USA	Positron emission tomography of human brain can monitor neuroinflammation and camp signaling: applications to alzheimer's disease and depression
October 2015	Pr Dennis PARKER	Utah Center for Advanced Imaging Research, Salt Lake City	MR-guided HIFU of the Brain : potentials and challenges
	Pr Franck SEMAH	CHRU Lille, France	Respective value of PET and MRI in the presurgical evaluation of patients with partial epilepsy
December 2015	Pr Maxime DESCOTEAUX	Sherbrooke connectivity Imaging Lab (SCIL), University Hospital of Sherbrooke, Canada	White matter bundle analytics: building atlases and tractometry in the space of streamlines
January 2016	Pr Philippe DOUEK	Cermep, centre d'imagerie du vivant, Lyon	le scanner spectral à comptage photonique
February 2016	Dr Anatol KONTUSH	INSERM Research Unit 1166, University Pierre and Marie Curie - Paris	nanoparticules pour le théranostic de l'athérosclérose
June 2016	Pr OBENAUS	Loma Linda University	Long-term Neuroimaging of Human Neural Stem Cells following Neonatal Hypoxic-Ischemic Injury
	Associate Pr Simon ESKILDSEN	Aarhus University	Capillary dysfunction in Alzheimer's disease
september 2016	Associate Pr Nicolas FARRUGIA	University of Brest	spatio temporal dynamics of functional connectivity extracted using dictionary learning approaches
October 2016	Dr. Florence DELMAS	Bruker	PET/MRI multimodal imaging : unparalleled accuracy

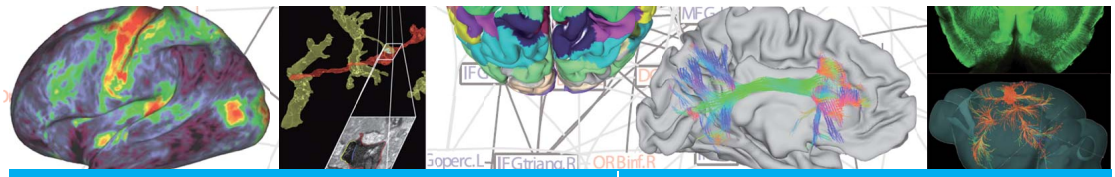
DATE	SPEAKER	ORGANIZATION	LECTURE
November 2016	Pr Lorenz HIRT	Unil-CHUV, Lausanne	Non invasive biomarkers in the ischemic mouse brain
	Dr Joao DUARTE	Laboratoire d'imagerie du métabolisme, Lausanne	Alterations of brain metabolism in type 2 diabetes: a magnetic resonance study in vivo
	Pr Luc PELLERIN	Unil-CHUV, Lausanne	Bolstering neuroenergetics as a neuro-protective strategy

Scientific animation and training

C.2 Scientific days



C.3 Summerschools



CONNECTOMICS 2014
THE WIRING DIAGRAM OF THE HUMAN BRAIN

1st International Summer School
September 22-26, 2014 - Bordeaux

A new discipline of modern neuroscience, the connectomic, examines the organization and functioning of the brain across all its anatomical and functional connections, namely the connectome. The understanding and optimal use of these methods require a multidisciplinary training for neuroscience researchers. This is the challenge of "CONNECTOMICS 2014", the first international summer school offering to the scientific community a state of the art of the advanced approaches currently used in determining the wiring diagram of the human brain, to deepen or to acquire new knowledge about a domain still not taught and booming: the human brain connectome.

Scientific committee

Katrin Amunts, Institute of Neurosci. and Medicine, Jülich, Germany; **Bernard Mazoyer,** Groupe d'Imagerie Neurofonctionnelle UMR5296, Bordeaux, France; **Christophe Mulle**, Interdisciplinary Institute of Neuroscience, UMR5297, Bordeaux, France; **Tomáš Paus**, Rotman Research Institute, Baycrest Centre, Toronto, Canada; **Laurent PETIT**, Groupe d'Imagerie Neurofonctionnelle UMR5296, Bordeaux, France.

Audience

The school will welcome 50 researchers, engineers, post-docs and end-term PhD interested in the topic of the connectome.

Information and Registration

http://connectomics2014.u-bordeaux.fr

deadline : 31st of July, 2014

Registration fees cover the courses, accommodation, coffee and lunch breaks.

500 € for researchers and engineers
300 € for post-docs and PhD students

Note that CONNECTOMICS 2014 is a Thematic School of the CNRS allowing no fees for personal employed by the CNRS.

Please note that the registration is mandatory to validate your application. Once your application is completed and has been evaluated, the organizing committee will let you know the final decision. If you are selected, registration process should be finalized through the payment of fee.

Program

September, Monday 22nd PM

Opening lecture
Connectome, connectomics: Origins by Olaf SPORNS

Microscopic structural connectome
- Neural circuit analysis with Brainbow by K. MATHO
- Activity-dependent labeling of memory engrams by S. RAMIREZ
- Advanced optical techniques for brain-wide imaging of neuronal activity by R. PREVEDEL

September, Tuesday 23rd

Microscopic structural connectome
- The secrets of neuronal circuits with recombinant rabies virus by A. FRICK
- Mapping synaptic function and connectivity in cortical cells by T. MARGRIE
- Optogenetic interrogation of valence circuits by A. BEYELER

Macroscopic structural connectome
- Connectomic approaches before connectome by M. THIEBAUT de SCHOTTEN
- The do's and don'ts of diffusion MRI by A. LEEMANS
- Advances in diffusion MRI acquisition and processing by S. SOTIROPOULOS
- Tractography with tractometer by G. GIRARD

September, Wednesday 24th

Macroscopic structural connectome
- dMRI in cortical gray matter and its validation with histology by A ROEBROECK
- Tractography against dissection by S. SARUBBO
- Insight into the development and maturation of the brain by T. PAUS

White matter as transport system
- White matter as a transport system by T. PAUS
- Titled coming soon by R. PAUTLER
- Titled coming soon by G. MORFINI

Introduction to Allen Institute resources
- Advancing neuroscience with the Allen Brain Atlas by T. GILBERT

September, Thursday 25th

Intrinsic connectivity
- Studying large-scale brain networks: Electrical stimulation & neural-event-triggered fMRI by N. LOGOTHETIS
- Temporal dynamics of the resting-state signal by C. CHANG
- Graph analysis of the connectome by S. ACHARD
- Extrinsic/intrinsic modular organization of the connectome by G. DOUCET
- Modular structure of fMRI networks in resting-state by D. MEUNIER
- Relation between r-fMRI and t-fMRI connectomes by F. HOFFSTAEDTER
- Cerebral Cortex Connectomics by M. HELMSTAEDTER

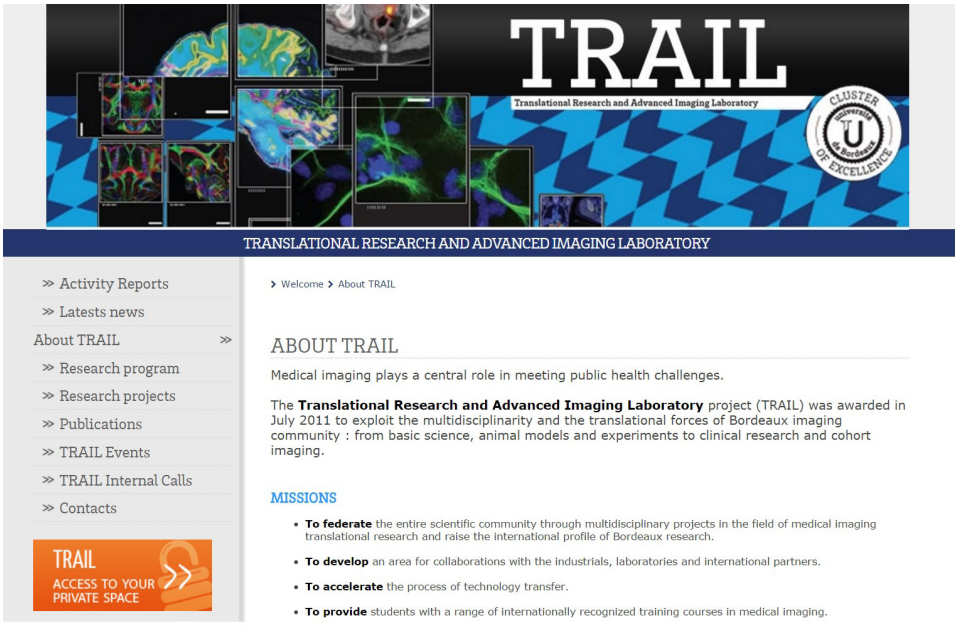
September, Friday 26th AM

Databasing
- The Brain CONNECT project by Y. ASSAF
- The BIL&GIN project : Investigating asymmetries by B. MAZOYER
- Genetics of the Connectome and the ENIGMA Project by P. THOMPSON

Scientific animation and training

C.4 Informing the Community

› The TRAIL website (http://trail.labex.u-bordeaux.fr/en/) is dedicated to inform about the LabEx, about events and internal calls ; in addition, a newsletter is sent to each Member of the Community to highlight specific event/ information. The Website and the Newsletter are both in english ; the graphical chart is common to all communication media of the LabEx



NEWSLETTER TRAIL#45

COMING EVENTS

7th December 2016 - Félix María Goñi Urcelay, Doctor Honoris Causa of the University

- **Starting at 11:00 in the conference room of the Labri, Campus of Talence.**
- Lecture from Pr. Goñi Urcelay, "Cell membranes: exploiting the limits" given in English, French and Spanish.
- Further details HERE.

SFRMBM symposium in Bordeaux : deadline for abstract submission soon !

- The next SFRMBM will be held in Bordeaux on 13-15 March 2017,
- Registrations are open, further details on the website : SFRMBM 2017

****Remember : DEADLINE for abstract submission on 10th December 2016****

HIGHLIGHT

Jérôme Badaut and Grégory Barrière (INCIA teams), coordinators of a recently funded Era-Net Neuron European project.

Jérôme Badaut *(Brain Molecular Imaging team, INCIA)* and Gregory Barrière *(Coordinations and Plasticities of Spinal Generators team, INCIA)* are the coordinators of the **TRAINS** consortium (Time dependent Remote Alterations after Injury to the Nervous System) recently awarded a **1.2 million Euros ERA-NET grant**.

The TRAINS consortium comprises internationally recognized experts in the field of brain and spinal cord injury; 6 teams from 5 countries : Drs Barrière and Badaut (France), Pr. Selmaj (Poland), Drs Dambrova & Zvejniece (Latvia), Dr Plesnila (Germany), Dr Schwartz (Israel), Dr Gressens (France).

C.5 Links with the international Master of BioImaging

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D/ Attractiveness

D.1 International academic partnership

WP	APPLIED MEDICAL AREA	TRAIL PROJECT	INTERNATIONAL COLLABORATION
1	Cardio	MRGHIFU	- NIH (Mickael Hansen): open source image reconstruction software (2015)
			- University of Utah: performing hardware and sequence adaptation for different MRI scanner
2	Cardio	NEWFISP	- University of Mons: contrast agents development for preclinical cardio imaging
			- University of Wisconsin: algorithms for 4D angiography
	Neuro	HRDTI	- Universidad de Valencia: extending HR-DTI method for q-ball and high b-value WDI
			- University of Sherbrooke: extending HR-DTI method for q-ball and high b-value WDI
		MDMRI	- Sherbrooke university, SCIL: Image processing, tractography, data analyses (2016)
4	Neuro	FITTING	- Complex Carbohydrate Research Center, University of Georgia, USA: chemical devolpment
	Onco	PRITOR	- INMAS (NewDehli India): preclinical micro TEP imaging
5	Cardio	MIMATHUMAB	- Autralian Center for Blood Disease, Monash University: Atheroma plaque PET imaging
			- Baker IDI Melbourne: Generation and testing of targeted MRI contrast agents and PET tracers
			- VIT University, India: apolipoprotein development
	Neuro	GMCOG	- Harvard, CNI: image post processing
			- Stanford University: analyses of thalamic data
		IBIONI	- BICAMS group: collaborations as part of consortium in cognitive impairment in MS
			- Harvard Medical School: post processing
			- Magnims Network, Buffalo University NY, Royal Holloway London, MS Center Amsterdam
			- Stanford: use of sequence development by Stanford for human application (2015)
		INNES	- UNIL-IP Lausane: providing anti-MCT2 antibodies
		SCICOG&REACTIV	- Magnims Network, Buffalo University NY, Royal Holloway London
		TBI	- Loma Linda university, California: vascular biology component
	Onco	BIOPSYPROS-TAPROBE	- University of Verona (Fracasso & Colombatti): antibodies engineering (2015)
6	Onco	MOD	- University of Alabama at Birmingham (Hassan Fathallah): glioblastoma models
			- University of Sherbrooke: PET phamacokinetic modeling
	Pneumo	NEKOMRI	- NIH: image reconstruction
7	Neuro	ABACI	- Washington University USA (HCP): population neuroimaging studies (multiple reference spaces)
		ACTE	- SRI International: acquisition, data analysis
		TRAIL&TRACKS	- Dpt of Neurosciences of Santa Chiara Hospital, Trento, Italy: white matter tracts analysis (2014)
			- Sherbrooke University (SCIL): tractography
			- University of Ferrara, Italy: white matter tracts analysis (2013)

D.2 Recruitments (funded by TRAIL)

POSITION	WP	TRAIL PROJECT	RECRUITEMENTS
Postdoctoral fellow	1	MRGHIFU	MARQUET Fabrice
			OZENNE Valéry
	2	HRDTI	BLED Emilie
		NEWFISP	RIBOT Emeline
			TROTIER Aurélien
	3	ONCOFLUX	RIZZITELLI Silvia
	4	TARGLIN	FEREIRO Isabel
	5	BIOPSYPROSTAPROBE	MASSANTE Cyril
			MAZZOCCO Claire
		IBIONI	CIAPPELLONI Silvia
		INNES	MAZUEL Leslie
		MIMATHUMAB	LORENZATO Cyril
		TRANSFEAR	ROZESKE Robert
			VALERIO Stéphane
	6	MOD	GROZAT Vladimir
		NEKOMRI	KRAHENBUHL Adrien
	7	ABACI	HERVE Pierre-Yves
		COBRASCAN	COSTE Florence
Doctoral fellow	1	MRGHIFU	JEANJEAN Pauline
	2	NEWFISP	TROTIER Aurélien
	3	TRAILDNP	KOONJOO Neha
			RIVOT Angelique
	4	IMMELAPT	KENNEL Sybille
		SUPSIFLU	TISSERAUD Marion
	5	GMCOG	KOUBIYR Ismail
		IBIONI	MUNSCH Fanny
		INNES	BLANC Jordy
		MIMATHUMAB	BONNET Samuel
		TBI	ICHKOVA Aleksandra
	6	MOD	PERIER Cynthia
	7	ACTE	ABDALLAH Majd
		TRAIL&TRACKS	HAU Janice

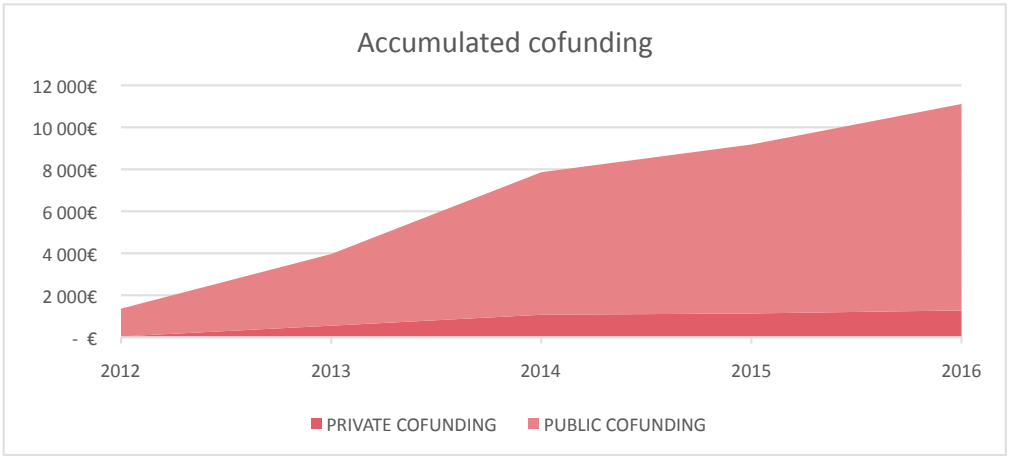
Attractiveness

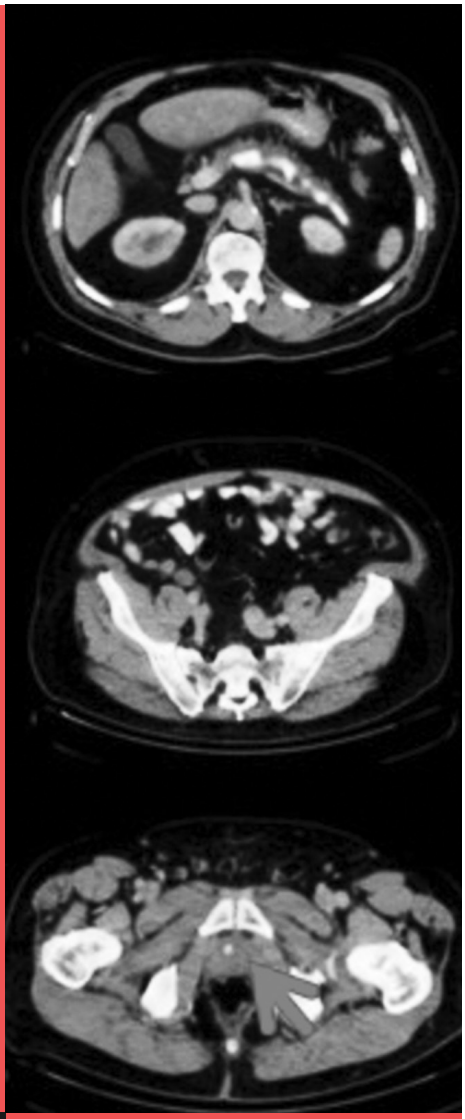
POSITION	WP	TRAIL PROJECT	RECRUITEMENTS
Engineer	3	ONCOFLUX	ZHENDRE Vanessa
	4	IMMELAPT	PAURELLE Olivier
		PIAF	MOUGEL Aurélie
	5	TBI	AUSSUDRE Justine
	6	ARM	LAFFITE Luc
		MOD	PIANET Vivien
	7	ABACI	DURIEZ Quentin
			HERVE Pierre-Yves
			LEROUX Gaelle
		ADPP	THEAUD Guillaume
Technician	4	IMMELAPT	BONAZZA Pauline
		NEPMIP	BAILLET Julie
	5	MIMATHUMAB	ANTOINE Ségolène
	7	ADPP	MAYOLINI Maxime

D.3 Co-funding

COFUNDING PER YEAR	2012	2013	2014	2015	2016	TOTAL
PRIVATE COFUNDING	40 000 €	511 459 €	520 000 €	62 100 €	145 000 €	1 278 559 €
PUBLIC COFUNDING	1 323 800 €	2 090 000 €	3 376 000 €	1 258 007 €	1 785 651 €	9 833 458 €
TOTAL	1 363 800 €	2 601 459 €	3 896 000 €	1 320 107 €	1 930 651 €	11 112 017 €

ACCUMULATED COFUNDING	2012	2013	2014	2015	2016
PRIVATE COFUNDING	40 000 €	551 459 €	1 071 459 €	1 133 559 €	1 278 559 €
PUBLIC COFUNDING	1 323 800 €	3 413 800 €	6 789 800 €	8 047 807 €	9 833 458 €
TOTAL	1 363 800 €	3 965 259 €	7 861 259 €	9 181 366 €	11 112 017 €





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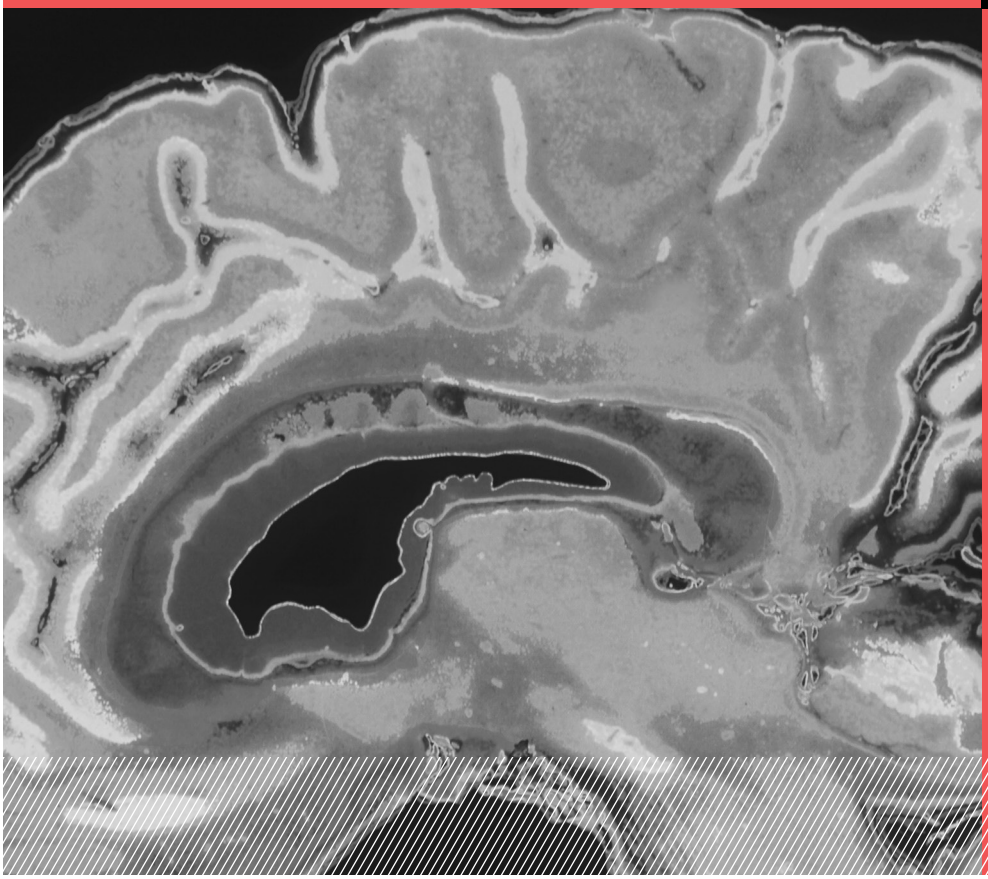

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Contact :
Jean-François Bauger: jean-francois.bauger@u-bordeaux.fr
Iris Lemoine: iris.lemoine@u-bordeaux.fr

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