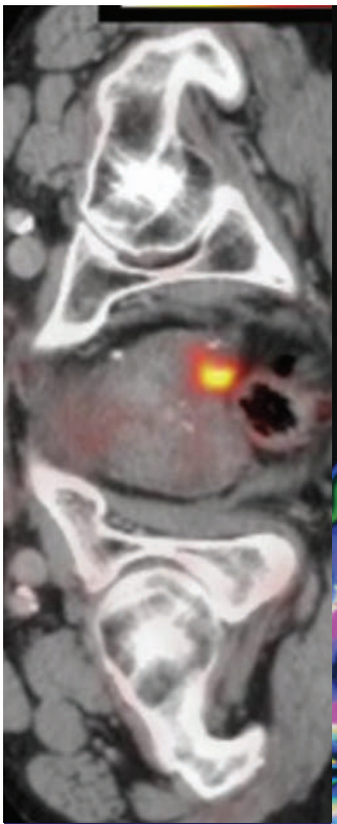
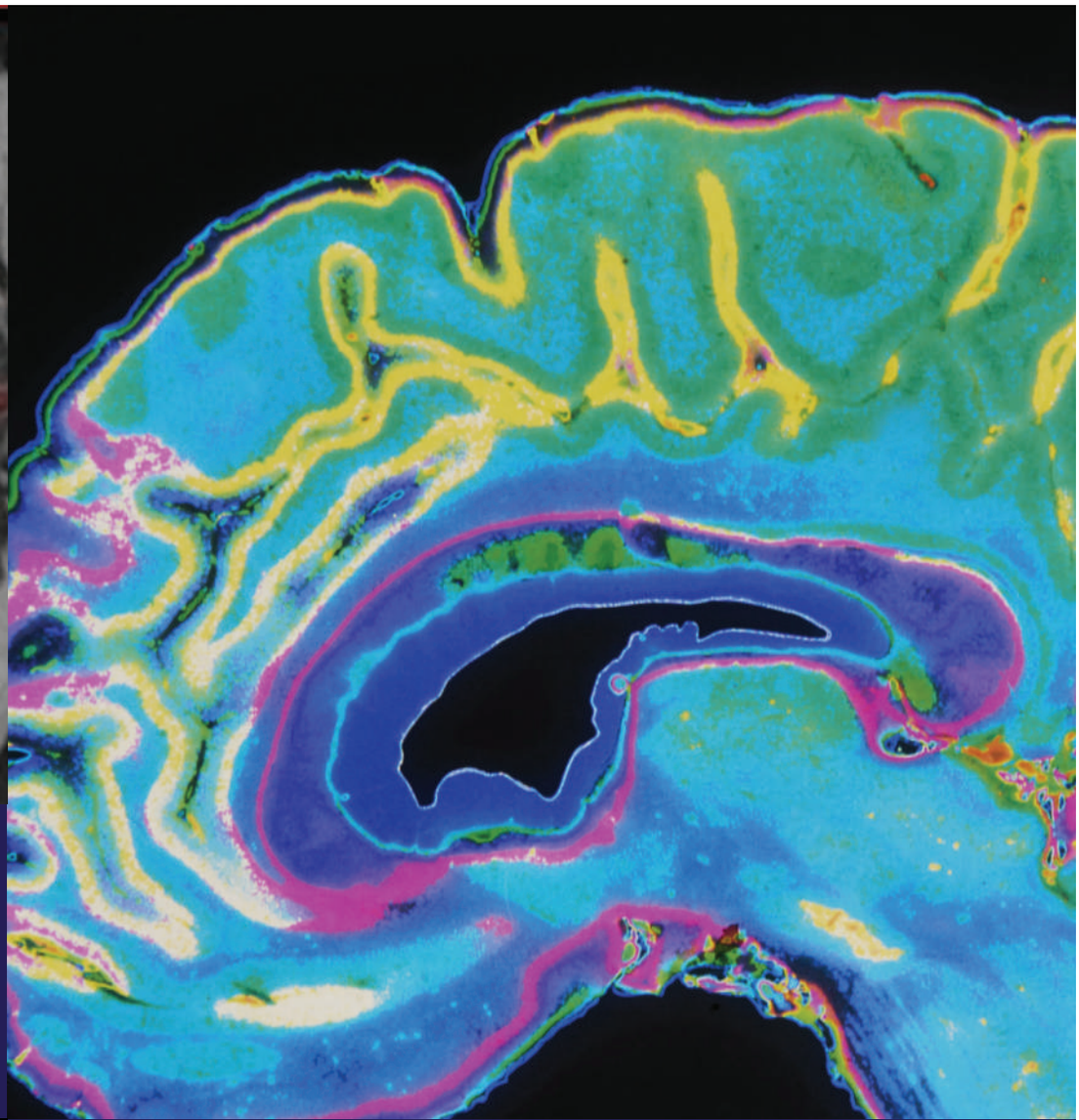
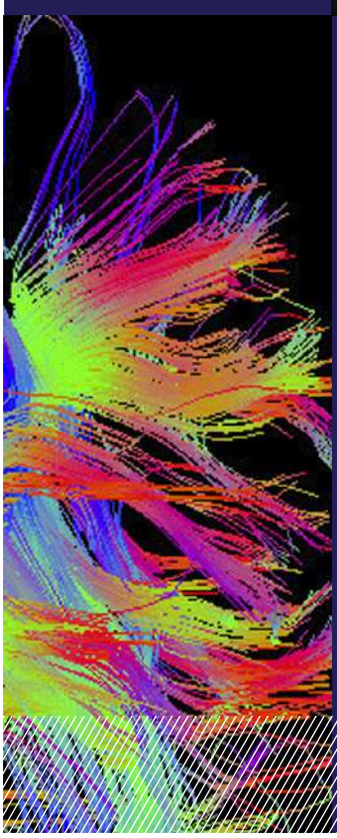




TRAIL

Translational Research and Advanced Imaging Laboratory



2011–2017 Activity Report

CLUSTER universitaire de Bordeaux OF EXCELLENCE

INVESTISSEMENTS D'AVENIR

université de BORDEAUX

cnrs

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Bordeaux INP AQUITAINE

Table of contents

PREPARING THE FUTURE

ANNEX

Activity Report

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 offer 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 addresses major health themes:

- Neurology
- Oncology
- Cardiology
- Pnemology
- 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 markers: 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 scientific 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

Preparing the future

2011-2017 Key figures

(see annex A.1 for details)

Research

285 scientists

41 funded research projects (6 M€)

10 top level research teams

126 publications quoting TRAIL

11 patents

Training

41 lectures by international speakers

4 intra-community scientific days

17 supported international symposiums

62 students in Master Program since 2012

Attractiveness

39 international academic collaborations

38 industrial collaborations

9 European projects

12.8 M€ of cofunding (1.4 M€ private)

9 visiting scholars

138 international communications

50 recruitments (PhD, post-doc, engineers, tech.)

Governance

58 steering committees

6 general assemblies

3 board of trustees meeting

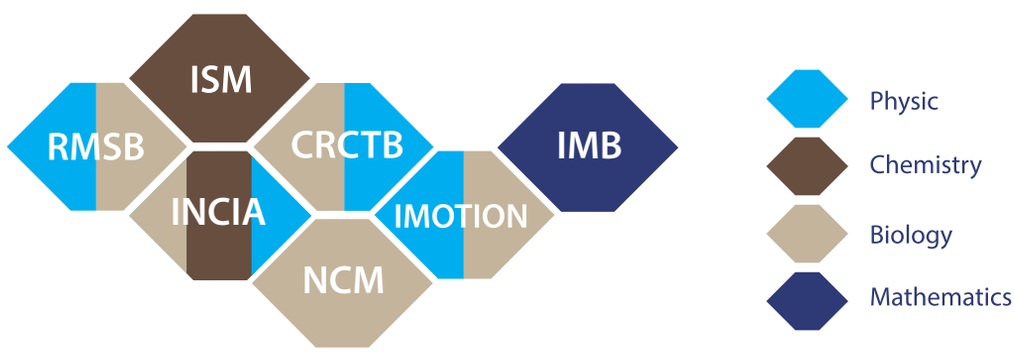
2 scientific advisory board meeting

1 mid-period audit from the french research agency

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: Center of Magnetic Resonance of Biological Systems
ISM: Molecular Sciences Institute (molecular imaging and photonic team and catalysis, synthesis and health team)
CRCTB: Cardio-Thoracic Research Center of Bordeaux (bronchial remodeling team and cardiac electrophysiology team)
INCIA: Aquitaine Institute for Cognitive and Integrative Neuroscience (neuroimaging and human cognition team and brain molecular imaging team)
NCM: Neurocenter Magendie (neuro-glia interactions team)
IMOTION: Molecular imaging and innovative therapeutics in oncology team
IMB: Mathematical Institute of Bordeaux (scientific calculation and modeling team)

The Community is composed of 285 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 four institutional trustees (University of Bordeaux, CNRS, INSERM, INP).

Board of Trustees

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

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.

Steering Committee

- 17 members: 10 representatives of laboratories, 5 representatives of thematic axes, 1 international representative 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.

Workpackages Coordinators

- 8 Coordinators (see annex A.3 for details);
- Role: Coordinators define scientific themes for calls guidelines, are part of the research project selection process, and are involved in scientific animation.

Governance

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.

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.

1.3 Administrative staff

- The administrative team is composed by the General Manager, Jean-François Bauger, and the Science Communication Manager, Hélène Katz. They are affiliated to the Direction des Grands Projets (DGP-RIPI);
- Role: the administrative team sets up procedures, implements actions, promotes the LabEx, and manages the budget in strong collaboration with the financial teams of the University of Bordeaux.
- The administrative team is accompagnied by RIPI teams regarding financial monitoring, organization of events, creation of graphical charters for communication documents, website redesigning, and benchmarking.

1.4 Monitoring and financial plan

Monitoring

- Developments are monitored by the Steering Committee and by the Director, in link with Workpackages Coordinators, with the IdEx Bordeaux and with the Trustees.
- The Steering Committee Members met 58 times over the 2011-2017 period. They are helped by i) Scientific Advisory Board Members for global scientific strategy (meetings in 2015 and 2017) and by ii) Workpackages 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 (three meetings : 2012, 2016 and 2017) and to the IdEx of Bordeaux. Main governance actions are presented to the TRAIL Community during annual General Assemblies.
- The financial team of the IdEx Bordeaux is in charge since 2014 of the management of TRAIL expenses, in deep integration with the TRAIL administrative team.

Financial plan

The financial plan was defined as follows for the 2011-2017 period:

TRAIL OBJECTIVES	STRATEGY	PROGRAM	2011	2012	2013	2014	2015	2016	2017	2011-2017
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€	200K€	700K€
		Research projects consolidation program				220K€	180K€	111K€	50K€	510K€
	Supporting new research projects	Federative and emerging research program	299K€	1 151K€	694K€	70K€	400K€	688K€	343K€	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€	262K€	223K€	790K€
			535K€	1 302K€	1 001K€	612K€	1 572K€	1 661K€	816K€	7 499K€

1.5 Support from 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.

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 9 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 LabEx 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 €).

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

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

IdEx Bordeaux managed the valorization of the research project SPINE developed in collaboration with Harvard University (see page 18).

In June 2017, IdEx Bordeaux organized the Week 26, an international innovation week composed of several events:

i) The Bordeaux-Euskampus Symposium 2017, which gave researchers in biophysics from the Basque Country and from Bordeaux the opportunity to exchange on potential future collaborations. The 2015 edition of the Symposium helped to establish links with an Ikerbasque researcher, whom founded a start-up (Fastbase), will start collaborations with French teams in 2018, and will open an antenna in Bordeaux;
ii) The Innovation Day on Sustainable Health, which allowed to present projects of economic valorization (MOD project);
iii) The Bordeaux-Kyoto Symposium, which was about industrial innovation in health and had a session dedicated to medical imaging.

1.6 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).

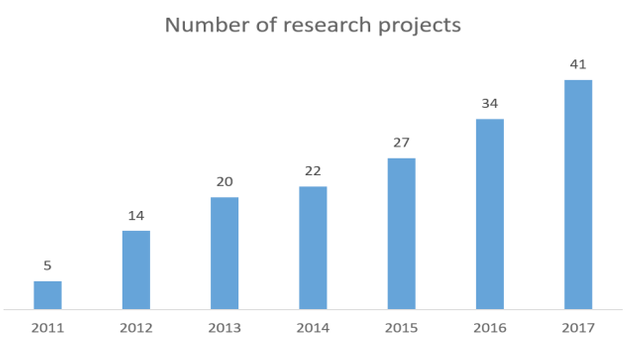
The funding from TRAIL aims at financing human resources costs and running costs. Financial support for equipment is limited to 15 000€ per project.
Each submission to a call is analyzed by 2 international scientific reviewers who assess the scientific originality of the project, the quality of the team 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.

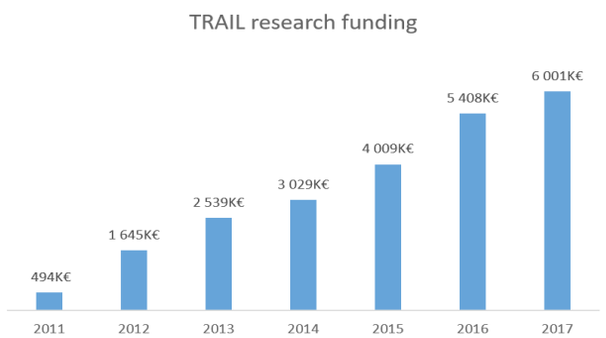
For the monitoring, project leaders report the achievements of research as follows:

- 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 2017, 41 research projects were funded, for a total budget of 6M€:

- 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 1 151K€;
- 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 1 399K€,
- In 2017: 7 emerging projects, 1 consolidated project and 2 Post-Doc funding, for a total budget of 592K€,





	Interventional imaging and MRI guided HIFU	New imaging sequences	DNP	Tracers & contrast agents	Biological Bio-imaging markers	Mathematic simulation and modeling	Cohort imaging methodology		
Neurology		179 600 €		48 800 €	1 406 231 €	49 924 €	572 330 €	2 256 885 €	37.6%
Oncology	80 000 €	45 850 €	482 500 €	834 000 €	185 000 €	530 000 €		2 157 350 €	36%
Cardiology	400 000 €	250 000 €		185 000 €	345 000 €			1 180 000 €	19.7%
Pneumology					40 000 €	35 000 €	234 448 €	309 448 €	5.2%
Nephrology					47 000 €	50 000 €		97 000 €	1.6%
	480 000 €	475 450 €	482 500 €	1 067 800 €	2 023 231 €	664 924 €	806 778 €	6 000 683 €	100%
	8%	8%	8%	18%	34%	11%	13%	100%	

2.2 Research portfolio

The input of the 41 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 (see annex B.1 for projects abstracts, and see annex B.2 for achievements).

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)

DEEP STROKE
DEEP Learning for prediction of long-term motor impairment after STROKE,
2017, 49 924 € (neuro)

BIOPSYPROSTAPROBE
Antibody-based fluorescence probe for biopsy guidance of prostate cancer,
2014, 185 000 € (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)

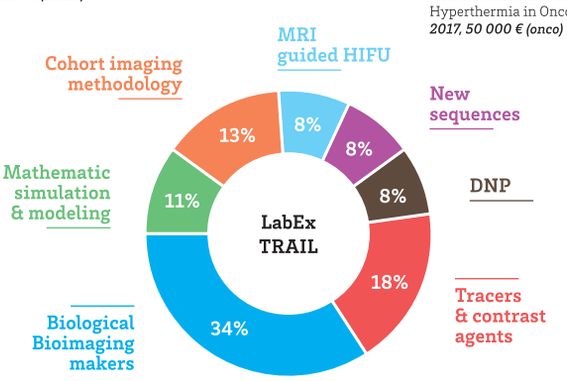
ABACI
Automated Brain anatomy softwares for cohort imaging,
2012, 314 830 € (neuro)

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)

NEMHO
NanoEmulsion for Magnetic Hyperthermia in Oncology,
2017, 50 000 € (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)

WHOBO-MP2RAGE
Whole body ultra-fast 3D T1 mapping with non-cartesian MP2RAGE sequences,
2017, 45 850 € (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)

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)

INNOVATHER
Innovative ways to enhance radiopharmaceutical therapy,
2017, 50 000€ (onco)

TBI
Longterm neurovascular unit changes after mild traumatic brain injury: potential biomarker & Vasc-TBI,
2015, 250 000 € (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)

MEMIM
Multiphoton endomicroscopy for metabolic imaging of macrophages in atherosclerosis,
2017, 50 000 € (cardio)

DIFFIR
Ex vivo DIFFusion-weighted MRI of renal Ischemia Reperfusion injury,
2017, 47 000 € (nephro)

BRAIN-RESV
Neuroprotective effect of resveratrol in hypoxic ischemic rat pups: how supplementation of the pregnant female could impact brain lesion of the pups ?,
2017, 50 000 € (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)

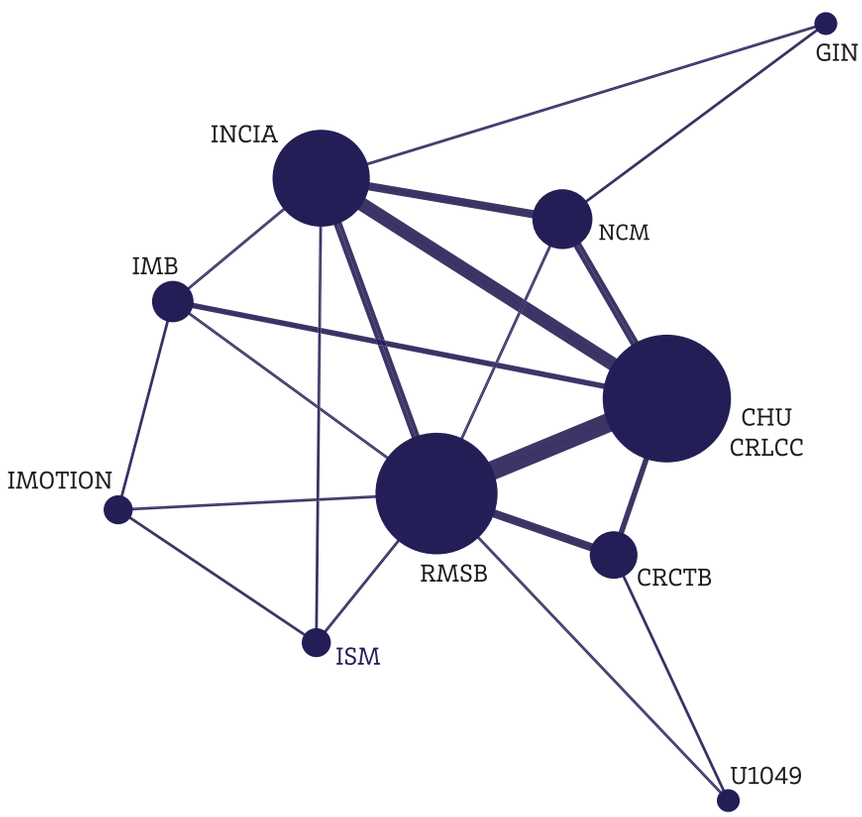
FITTING
18F-Bioorthogonal probe for imaging traumatic brain injury glycol-biomarkers,
2016, 48 800 € (neuro)

Research achievements

2.3 Interdisciplinarity

Research in TRAIL is based on multidisciplinary teams:

- 78% of TRAIL funded federative projects (and 30% of emerging projects) rely, at least, on expertises of 2 different CorePartners;
- 80% of TRAIL funded projects involve clinicians from the beginning of the project.



2.4 Imaging platforms

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.

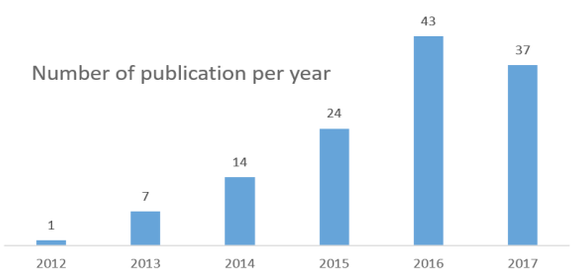
2.5 Scientific communication

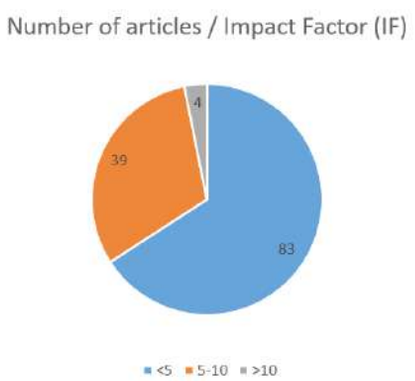
Publications in peer-reviewed journals

- TRAIL researchers have published 126 publications quoting TRAIL over the 2011-2017 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,...

- 46 TRAIL publications belong to the 10% of most quoted publications in the world over the 2011-2017 period;
- The average Field-Weighted Citation Impact is 1,57[1];
- Publications costs of TRAIL quoted publications are co-funded by the LabEx.

[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)





Scientific communications

Researchers from the Community have given 138 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,...

2.6 Patents and Software Protection Agency recordings

By the end of 2017, 11 patents and 4 Software Protection Agency recordings issued from TRAIL have been registered (see annex B.4 for details):

6
patents on cardiology topics

1
patents on neurology topics

3
patents (and 4 Software Protection Agency recordings) 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.

Scientific animation and training

3.1 TRAIL scientific events in Bordeaux

Conferences

TRAIL teams invited 41 international speakers to give lectures in Bordeaux (see annex C.1 for details). For example, in 2017, 4 lectures were given: B Larijani, F Paul, F Chaumard and B Tavitian.

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 (see annex C.2 for details).

Assises

The members of the Community met at the first TRAIL Assises in June 2017 to discuss the future of the LabEx after 2020.

Scientific days

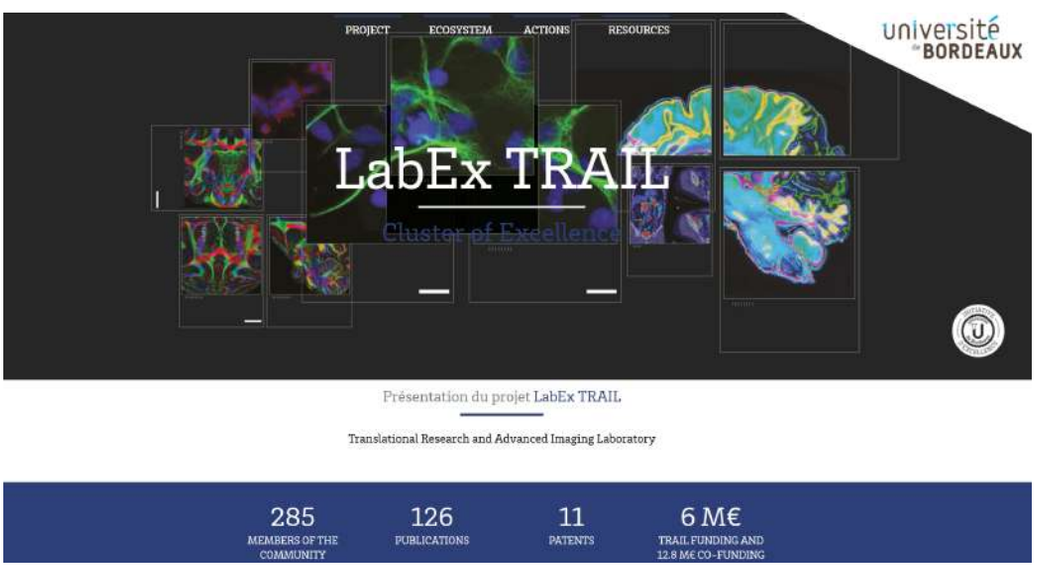
TRAIL research projects are presented by project leaders to the Community during annual "intra-community scientific days", and during "Workpackage scientific meeting" (see annex C.3 for details).

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.4 for details).

3.2 Informing the Community

The TRAIL website (trail.labex.u-bordeaux.fr) 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.5 for details). In October 2017, the website was entirely redesigned. It is now more modern and offers an easier navigation as well as a faster access to information.



3.3 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	Cosine 6 (May 2016)	Medicine and digital
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	GECO57 (Ascain, Aug 2016)	Organic chemistry
2016	ESUR (Bordeaux, Sept 2016)	European Symposium on Urogenital Radiology
2017	SFRMBM (Bordeaux, March 2017)	MRI, MR spectroscopy
2017	NeuroFrance 2017 (Bordeaux, May 2017)	Neurosciences
2017	5e Ecole d'imagerie du Petit animal appliquée au Cancer (Bordeaux, June 2017)	Oncology preclinical imaging
2017	ERANET (Bordeaux, June 2017)	Neuroimaging changes after acute brain injuries to evaluate the remote plasticity
2017	Aptamers in Bordeaux (Bordeaux, Sept 2017)	Aptamers biology, chemistry & technology
2017	SFNano 2017 (Bordeaux, December 2017)	Nanomedicine

3.4 Links with the international Master of Bio-Imaging

In collaboration with the University of Laval in Quebec and the University of Mons in Belgium, the Master of Bio-Imaging 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.

Since its last accreditation, the degree has been renamed to Master of Health Engineering. In 2017, 45 students were registered (20 students in the first year and 25 in the second year of the degree).

3.5 Links with the FLI network

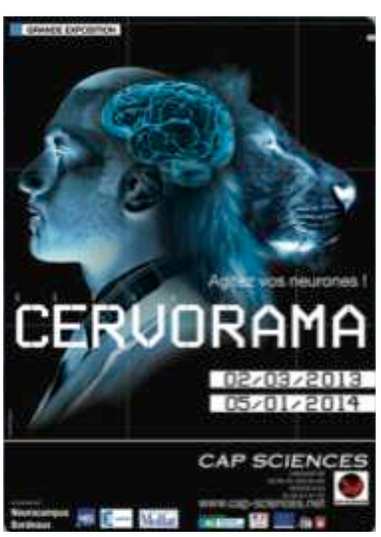
The French Life Imaging (FLI) national infrastructure (Bordeaux, Grenoble, Lyon, Marseille, Paris) is reorganizing the educational programs for students and young researchers to make a national and international offer. TRAIL, as a member of FLI, participates to this program.

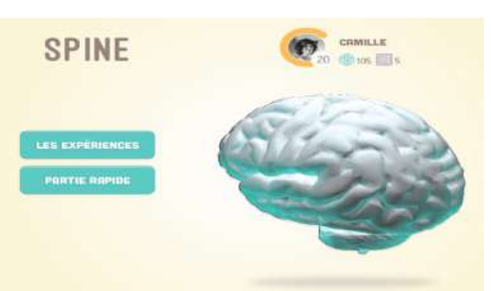
Scientific animation and training

3.6 Knowledge dissemination to the 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 citizen science game project called SPINE 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. In 2017, the dissemination to the general public was organized around 3 conferences in Bordeaux: Chemistry Association Bordeaux evening "From chemistry to health", "University for All" conference "Modeling and cancer" and Journée de la recherche "Simulation in oncology". Also, a researcher participated in the elaboration of a chapter of the book "Thoracic imaging" (ed. Masson).





4/ Attractiveness

4.1 International academic partnerships

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 50 publications quoting TRAIL (42.7% 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 9 european projects, increasing its international visibility:

- 2017: ERA-net TRANSCAN ; COST Action;
- 2016: ERA-net NEURON-Trains ; COST Action ; IMI Beat-DKD;
- 2015: FLAG-ERA JTC Multilateral (The 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, 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 and IdEx Bordeaux welcomed 9 international visiting scholars since 2014:

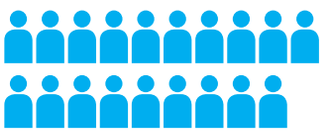
- Pr Troels Skrydstrupi (Aarhus University, Copenhagen);
- Pr Charles Guttmann (University of Harvard, Boston);
- Pr Denis Parker (University of Utah, Salt Lake City);
- Pr Juan P. Bolanos (The Institute of Functional Biology and Genomics, Salamanca);
- Pr Anil Kumar Mishra (Institute of Nuclear Medicine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

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

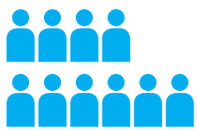
- Clément Morgat: mobility to INMAS, India;
- Julien Jouganous: mobility to MacGhill University, Canada;
- Gisèle Clofent-Sanchez: mobility to the University of Melbourne, Australia;
- Thomas Tourdias: mobility to Stanford University, USA;
- Thomas Cornilleau: mobility to Aarhus University, Denmark;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

4.4 Recruitments

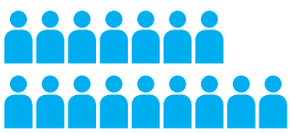
50 persons have been recruited by TRAIL research projects (see annex D.2 for details):



19
post-doctoral fellows



10
engineers



16
doctorals fellows

5
technicians

4.5 Collaboration with industrials

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

TRAIL Workpackages and research projects show the excellence of Bordeaux research in medical imaging but they are competing with major international research centers as well as industrial research. It is among the TRAIL objectives 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, or through a publication (5 TRAIL quoting publications are in collaboration with industrials).

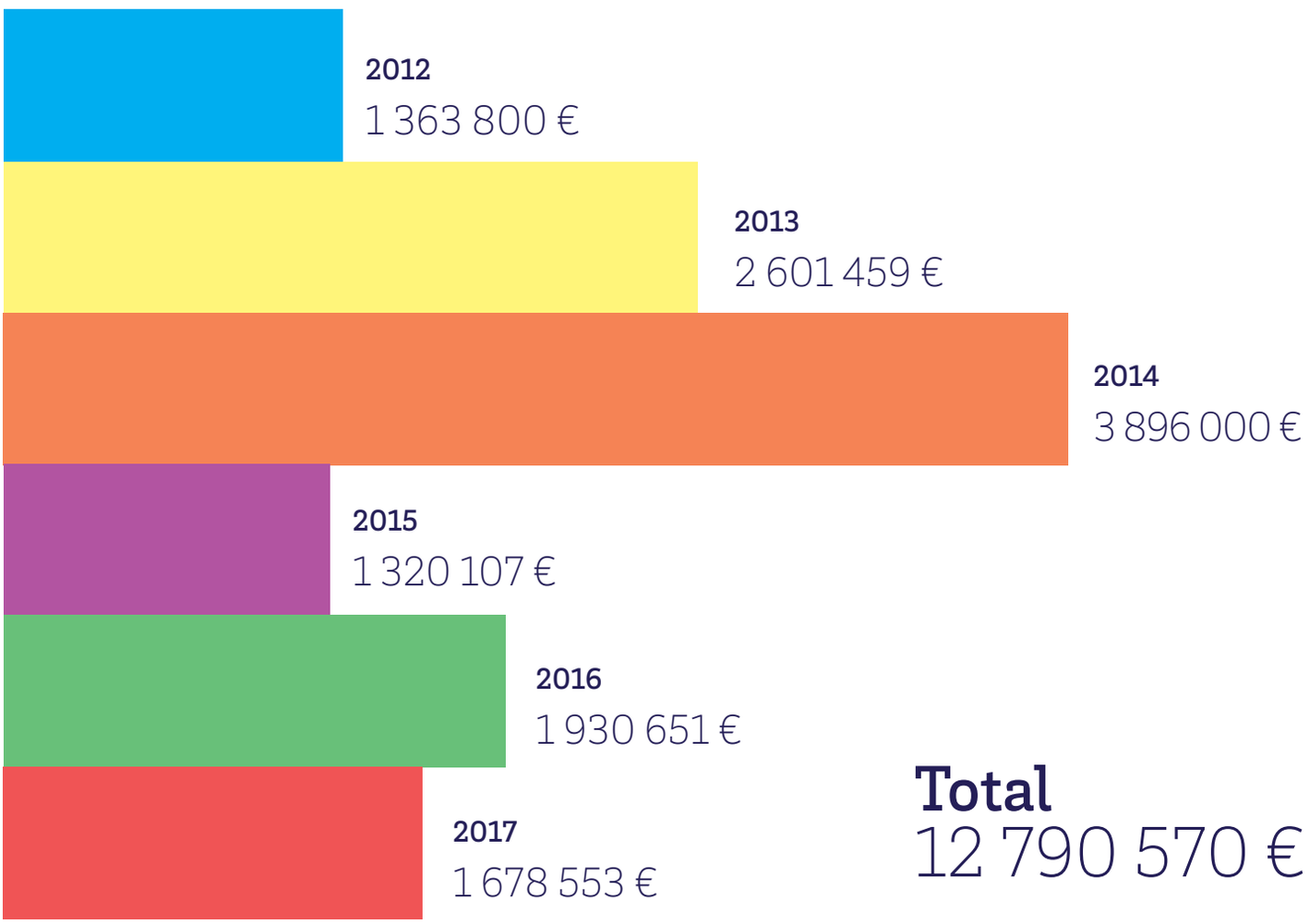
26 companies have been involved in TRAIL research projects since 2011 through direct cofunding, human resources and free use of their products/equipments:

- ALPhANOV: compact laser source development;
- 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;
- CANON MEDICAL SYSTEMS: MS exploration;
- DESKI: deep learning models;
- 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 sequencing;
- 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;
- SOPHIA GENETICS: radiomics and genetics;
- SUPERSONIC IMAGING: imaging equipment prototyping;
- TEVA: support for neuroinflammation clinical studies;
- UNITHER: drug efficiency study;
- VERMON: bimodal endorectal probe.

Attractiveness

4.6 Cofunding

TRAIL research projects leaders have reinforced their projects budgets with a total of 12.8M€ of cofunding, including 1.42M€ from the private sector (see annex D.3 for details):



Annex

Annex

A/ Governance

A.1 TRAIL main figures per year

			TOTAL	2011	2012	2013	2014	2015	2016	2017
RESEARCH	RESEARCH PROJECTS	Number of new projects	41	5	9	6	2	5	7	7
		Number of new "emerging" projects	23	0	5	2	2	3	4	7
		Number of new "federative" projects	18	5	4	4	0	2	3	0
		Research budget	6 000 683 €	493 971 €	1 150 866 €	894 448 €	490 000 €	979 618 €	1 399 006 €	592 774 €
		Research budget for "emerging" projects	1 636 174 €		150 000 €	160 000 €	335 000 €	260 000 €	388 400 €	342 774 €
		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	5
		Number of WP of TRAIL matrix covered by granted research projects	7 (100%)	4	6	7	7	7	7	7
		WP1 budget	480 000 €		30 000 €	140 000 €		100 000 €	160 000 €	50 000€
		WP2 budget	475 450 €		280 000 €	100 000 €			49 600 €	45 850 €
		WP3 budget	482 500 €	97 500 €		180 000 €	45 000 €	160 000 €		
		WP4 budget	1 067 800 €	119 000 €	250 000 €	60 000 €	45 000 €	345 000 €	198 800 €	50 000€
		WP5 budget	2 023 233 €	179 971 €	311 036 €	100 000 €	300 000 €	344 618 €	390 608 €	397 000€
		WP6 budget	664 924 €			180 000 €	35 000 €		400 000 €	49 924 €
		WP7 budget	806 778 €	97 500 €	279 830 €	134 448 €	65 000 €	30 000 €	200 000 €	
		EA 7435 (IMOTION) budget	97 000 €							97 000 €
		IMB budget	580 000 €			180 000 €			400 000 €	
		INSERM U1049 budget	30 000 €		30 000 €					
		INSERM U1215 (MAGENDIE) budget	820 578 €	130 000 €	281 036 €		100 000 €	59 618 €	200 000 €	49 924 €
		U1045 (CRCTB) budget	709 448 €			274 448 €	35 000 €	100 000 €	300 000 €	
		UMR 5287 CNRS (INCIA) budget	898 400 €		280 000 €	30 000 €		240 000 €	198 400 €	150 000€
		UMR 5296 (GIN) budget	412 330 €	97 500 €	249 830 €		65 000 €			
		UMR 5536 (RMSB) budget	2 008 929 €	147 471 €	310 000 €	380 000 €	245 000 €	480 000 €	150 608 €	295 850 €
		UMR5255 (ISM) budget	444 000 €	119 000 €		30 000 €	45 000 €	100 000 €	150 000 €	
	SCIENTIFIC COMMUNICATION	Number of publications quoting TRAIL	126		1	7	14	24	43	37
		Number of publications showing an impact factor <5	83		1	5	10	17	24	26
		Number of publications showing an impact factor between 5 and 10	39			2	4	5	18	10
		Number of publications showing an impact factor >10	4					2	1	1
		Number of publications of WP1 projects	7					1	2	4
		Number of publications of WP2 projects	27			2	4	10	6	5
		Number of publications of WP3 projects	8			1	2	1	2	2
		Number of publications of WP4 projects	23		1	1	2	1	10	8
		Number of publications of WP5 projects	43			3	5	8	16	11
		Number of publications of WP6 projects	9					2	2	5
		Number of publications of WP7 projects	9				1	1	5	2
		Number of publications of EA IMOTION projects	5						2	3
		Number of publications of IMB projects	4					2	2	2
		Number of publications of INSERM U1215 (MAGENDIE) projects	24			1	4	5	9	5
		Number of publications of U1045 (CRCTB) projects	12					1	5	6
		Number of publications of UMR 5287 (INCIA) projects	18				3	1	9	5
		Number of publications of UMR 5536 (RMSB) projects	46			5	7	14	10	10
		Number of publications of UMR 5255 (ISM) projects	15		1	1		1	6	6
		Number of scientific communications during international events	138	0	0	9	18	27	40	44

A/ Governance

			TOTAL	2011	2012	2013	2014	2015	2016	2017
TRAINING	SCIENTIFIC EVENTS	Number of supported scientific events	17	0	2	0	1	3	9	6
		TRAIL cofunding	86 900 €	- €	14 400 €	- €	15 000 €	19 000 €	8 500 €	30 000 €
	TRAIL EVENTS IN BORDEAUX	Number of "Scientific Days"	4	0	0	1	1	1	1	0
		Number of lectures by international speakers in Bordeaux	41	0	1	10	5	12	9	4
	MASTER BIO-IM.	Number of students	62	nd	14	15	10	11	12	-
ATTRACTIVENESS	SCIENTIFIC COLLABORATIONS	Number of new academic international collaborations	39	5	14	4	2	1	7	6
		Number of new academic national collaborations	37	7	7	8	3	1	5	6
		Number of new european project (includ. ERC)	11	0	1	2	0	2	4	2
		Number of visiting scholars (IdEx program)	11	0	0	0	3	2	3	3
		Number of outgoing mobilities	7	0	0	1	0	4	1	1
	COFUNDING	Budget	12 790 570 €	- €	1 363 800 €	2 601 459 €	3 896 000 €	1 320 107 €	1 930 651 €	1 678 553 €
		Cofunding budget/TRAIL research budget	213%	0%	119%	291%	795%	135%	138%	283%
	INDUSTRIAL VALORIZATION	Number of patents	11	0	0	0	7	2	1	1
		Number of Software Protection Agency recordings	4	0	0	0	0	0	4	0
		Private cofunding	1 416 559 €	- €	40 000 €	511 459 €	520 000 €	62 100 €	145 000 €	138 000 €
		Number of industrials in link with TRAIL	26	5	9	3	1	3	0	5
		Number of new collaborations with industrials	38	5	10	6	1	4	7	5
	RECRUITMENTS (FUNDED BY TRAIL)	Number of post-doctoral fellowships	19	0	1	1	6	4	5	2
		Number of doctoral fellowships	16	0	3	0	2	3	6	2
		Number of engineers	10	0	0	1	3	2	4	0
		Number of technicians	5	0	0	0	1	1	3	
		Number of administrative staff	2	-1	1	0	0	0	0	+1
		Total number of recruitments	52	1	6	2	12	9	18	4
		% of research budget dedicated to human resources	68%	76%	47%	64%	75%	83%	78%	55%
GOVERNANCE	BUDGETS AND GOVERNANCE MEETINGS	Number of Steering Committees	58	4	9	10	8	9	9	9
		Number of Scientific Advisory Boards	2	0	0	0	0	1	0	1
		Number of Boards of Trustees	3	0	1	0	0	0	1	1
		Number of Annual General Assemblies	7	1	1	1	1	1	1	1
		Number of Assises	1	-	-	-	-	-	-	1
		Number of audits by the national research agency	1	0	0	0	0	1	0	0
		Number of CorePartners - Number of teams	7-10	8-8	8-8	8-8	8-8	8-8	7-10	7-10
		Number of persons in the Community	285	240	240	240	240	240	260	285
		Global TRAIL budget	7 533 974 €	534 671 €	1 301 511 €	1 001 185 €	646 879 €	1 572 489 €	1 661 465 €	815 774 €
		Research budget	6 000 683 €	493 971 €	1 150 866 €	894 448 €	490 000 €	979 618 €	1 399 006 €	592 774 €
		Budget dedicated to governance, training, MRI time for the Community	1 533 291 €	40 700 €	150 645 €	106 737 €	156 879 €	592 871 €	262 459 €	223 000 €

A.2 The Community

The Community is composed of 285 persons: researchers, clinicians, post-docs, PhD students, engineers working on complementary themes.

POSITION	NUMBER OF PERSONS
Researchers/clinicians	144
Postdoctoral fellows	41
Doctoral fellows	44
Engineers	40
Technicians	16
TOTAL	285

A.3 Steering Committee and Workpackage Coordinators

STEERING COMMITTEE					
Function	Unit	Director	Thematics	Team (N=10)	Representative (N=17)
LabEx Director					V Dousset
CorePartner representatives	CRCTB	R Marthan	Bronchial remodeling	P Berger	P Berger
			Cardiac electrophysiology	M Haïssaguerre	H Cochet
	IMOTION	F Couillaud	Molecular imaging and innovative therapies in oncology	F Couillaud	F Couillaud
	IMB	JM Couveignes	Scientific calculation and modeling	Y Coudière	O Saut
	INCIA	JR Cazalet	Neuroimaging and human cognition	I Sibon & J Swendsen	I Sibon
			Brain molecular imaging	J Badaut	J Badaut
	ISM	E Fouquet	Molecular imaging and photonic	M Blanchard-Desce	Y Crémillieux
			Catalysis, Synthesis and Health	E Fouquet	E Fouquet
	RMSB	S Miraux	Center for magnetic resonance of biological systems	S Miraux	AK Bouzier-Sore
	MAGENDIE	PV Piazza	Glia-neuron interactions	S Oliet	A Ruet
Thematics representatives	Neurology				G Catheline
	Oncology				J Palussiere
	Cardiology				M Montaudon
	Pneumology				G Dournes
	Nephrology				N Grenier
International representative					L Pellerin

WORKPACKAGE COORDINATORS (N=8)	
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	P Coupé
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 Workpackages 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 supports 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 labeling 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, thanks to an adequate selection of projects and partnerships (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 jury from the French National Research Agency, June 2015.

B/ Research achievements

B.1 Research portfolio: project abstracts and publications

B.11 Workpackage 1 – "Interventional imaging and MRI guided HIFU"

HIFU

High-Intensity Focused Ultrasound

■ Klaus Petry	■ CorePartner "Neuroinflammation, imaging and therapy of multiple sclerosis" Inserm unit U1049	
■ 2012	■ Oncology	■ 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

■ Bruno Quesson	■ CorePartner Bordeaux Cardio-Thoracic Research Center (CRCTB, U1045)	
■ 2013	■ Oncology-cardiology	■ 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;
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- Feasibility of real-time MR thermal dose mapping for predicting radiofrequency ablation outcome in the myocardium in vivo, Solenn Toupin , Pierre Bour, Matthieu Lepetit-Coiffé, Valéry Ozenne, Baudouin Denis de Senneville, Rainer Schneider, Alexis Vaussy, Arnaud Chaumeil, Hubert Cochet, Frédéric Sacher, Pierre Jaïs, and Bruno Quesson, Journal of Cardiovascular Magnetic Resonance, 2017;
- Impact of surface grafting density of PEG macromolecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors, Laurent Adumeau, Coralie Genevois, Lydia Roudier, Christophe Schatz, Franck Couillaud, Stephane Mornet, BBA - General Subjects, 2017;
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NEMHO

NanoEmulsion for Magnetic Hyperthermia in Oncology

■ Sylvie Crauste-Manciet	■ CorePartner Molecular IMaging and Innovative Therapeutics In Oncology (EA 7435 IMOTION)	
■ 2017	■ Oncology	■ TRAIL funding: 50 000 €

Magnetoactivable Thermogenic Nanoparticles (MTN) as heat source appeared as an attractive method for local cancer treatment especially for deep-seated and poorly accessible tumors. Injection of MTNs into tumors and their subsequent heating using an alternating magnetic field (so called magnetic hyperthermia) has been developed as a cancer treatment for several decades. In clinical practices (Nanotherm®, Magforce®) as well as preclinical experiments (Sandre et al 2017), huge amount of MTNs closed to the limit of dispersability of the magnetic nanoparticles in biological media are required to achieve the in vivo hyperthermia. More efficient magnetic MTNs, exhibiting higher SAR (specific heating power) may be relevant for further clinical applications. This can be performed by optimizing nanoparticle chemical composition and size but also, in a more original way, by controlling the heat transfers between MTN and the surrounding aqueous medium. The present project by combining individual competencies of different partners aims to generate a new type of MTN by loading the oily nanodroplets of biocompatible water-in-oil nanoemulsion with iron oxide nanoparticles and to characterize their heating properties before studying in vivo by imaging their use for magnetic hyperthermia applications.

Research achievements

B.12 Workpackage 2 – "New sequences"

HRDTI

High Resolution DTI method

Bassem Hiba	CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)	
2012	Neurology	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;
- 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, 2015.
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- 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, 2016;
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- VolBrain: An Online MRI Brain Volumetry System, José V.Manjón and Pierrick Coupé, Frontiers in Neuroinformatics, 2016;
- CERES: A new cerebellum lobule segmentation method, Jose Romero, Pierrick Coupe, Remi Giraud, Vinh-Thong Ta, Vladimir Fonov, Min Tae Park, Mallar Chakravarty, Aristotle Voineskos, Jose Manjon, NeuroImage, 2017;
- HIPS: A new hippocampus subfield segmentation method, Jose E. Romero, Pierrick Coupe, Jose V. Manjon, Neuroimage, 2017;
- Towards a Unified Analysis of Brain Maturation and Aging across the Entire Lifespan: A MRI Analysis, Pierrick Coupé, Gwenaelle Catheline, Enrique Lanuza, and Jose Vicente Manjon, Human Brain Mapping, 2017;
- SuperPatchMatch: An Algorithm for Robust Correspondences Using Superpixel Patches, Rémi Giraud, Vinh-Thong Ta, Aurélie Bugeau, Pierrick Coupé, and Nicolas Papadakis, IEEE, 2017.

MDMRI

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

■ Bassem Hiba	■ CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)	
■ 2016	■ Neurology	■ 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.

Research achievements

NEWFISP

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

- Sylvain Miraux
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2012
- Cardiology
- 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:

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- 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, 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;
- 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, 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;
- In vivo MEMRI characterization of brain metastases using a 3D LookLocker T1-mapping sequence, Charles R. Castets, Néha Koonjoo, Andreea Hertanu, PierreVoisin, Jean-Michel Franconi, Sylvain Miraux & Emeline J. Ribot, Nature Scientific Reports, 2017.

WHOBO-MP2RAGE

Whole body ultra-fast 3D T1 mapping with non-cartesian MP2RAGE sequences

■ Emeline Ribot Aurélien Trotier	■ CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)	
■ 2017	■ Oncology	■ TRAIL funding: 45 850 €

The Magnetization-Prepared 2 Rapid Gradient Echo (MP2RAGE) sequence is getting more used in clinics due to the increased contrast at 3T (and higher) between grey and white matters in the human brain and due to the rapid acquisition of 3D images. Nevertheless, this sequence has never been performed in organs affected by motion, like in the abdominal cavity. This sequence could be very useful to detect and quantify pathologies that affect several organs throughout the body. It is particularly the case in oncology where metastases are disseminated in the whole body. An easy detection and segmentation of disseminated metastases in parallel with a rapid T1 quantification on these structures would be a tremendous asset in fundamental research to get more knowledge in the metastatic process and in clinics for a better diagnosis and prognosis of cancer patients. For now, the use of the MP2RAGE sequence at high magnetic field (≥3T) and its application on the whole-body of patients and mice is challenging in its current scheme. Consequently, the goal of our project is to develop non-cartesian MP2RAGE sequences by using radial encoding. Various exotic and pseudo-random encoding schemes will be tested and combined to a fat-suppression module and a self-gating technique in order to obtain artifact-free 3D T1 maps of the whole body in short acquisition time. This sequences will be first implemented on a 7T preclinical scanner in order to perform 3D mouse whole-body imaging. The optimization of the sequence parameters should enable the detection, segmentation and the T1 quantification of disseminated metastases in the brain, the lungs, the liver and the bone of mice and thus perform longitudinal analyzes of metastases. In parallel, this innovative sequence will beimplemented on a clinical 3T scanner to obtain unprecedented 3D T1 maps of abdominal imaging of healthy volunteers.

■ B.13 Workpackage 3 – "DNP"

ONCOFLUX

Metabolic flux MR imaging in tumors

■ Yannick Cremillieux	■ CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)	
■ 2013	■ Oncology	■ 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.

Research achievements

Publications quoting TRAIL:

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- Orotracheal manganese-enhanced MRI (MEMRI): An effective approach for lung tumor detection Andrea Bianchi, Oliviero L. Gobbo, Sandrine Dufort, Lucie Sancey, François Lux, Olivier Tillement, Jean-Luc Coll, Yannick Crémillieux, NMR in Biomedicine, 2017.

TRAILDNP

In vivo DNP in mice at 0,2T

■ Eric Thiaudiere	■ CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)	
■ 2011	■ Neurology	■ 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.

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- 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;
- 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;

B.14 Workpackage 4 – "Tracers and constrast agents"

FITTING

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

- Frédéric Friscourt
- CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2016
- Neurology
- 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.

Publications quoting TRAIL:

- Aquaporins through the brain in health and disease: From water to gas movements, Friscourt F, Badaut J, J Neuro Res. 2017.

IMMELAPT

SPECT molecular Imaging and optimized apatmers for tumor detection

- Jean-Jacques Toulmé
- CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2012
- Oncology
- 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.

Publications quoting TRAIL:

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Research achievements

INNOVATHER

Innovative ways to enhance radiopharmaceutical therapy

■ Clément Morgat	■ CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)	
■ 2017	■ Oncology	■ TRAIL funding: 50 000 €

Neuropeptide receptors can be highly expressed on the cell surface of tumor cells, paving the way to their visualization with Positron Emission Tomography (PET) using analogues radiolabeled with 68Ga, 64Cu or 18F, but also to select patients who can benefit from radiopharmaceutical therapy using similar analogues radiolabeled with 177Lu or 90Y. An example has been the development of somatostatin radio-analogues for imaging (68Ga-DOTATOC, 68Ga-DOTATATE) and therapy (90Y-DOTATOC, 177Lu-DOTATATE) of neuroendocrine tumors leading to impressive results(1,2). This concept has gained interest with the discovery of other neuropeptides and their receptors overexpressed in diverse tumors(3). In preliminary experiments, we have identified the neuropeptide-Y receptor 1 (Y1) as a potential therapeutic target in breast cancer. On the other hand, our team has demonstrated that the radioisotope terbium-161 (161Tb) might deliver higher doses to micrometastatses than 177Lu. In this project, we aim at investigating the possibility offered by Y1 targeting in breast cancer and developing new radiolabeled Y1 analogues for imaging and therapy. To achieve these objectives, we will identify Y1 in a large bank of more than 1400 tumors, in parallel we will develop and investigate novel Y1 analogues suitable to deliver 161Tb to the nucleus, and finally we would understand the mechanism of action of such membrane active peptide.

NANOMULTIMAG

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

■ Mireille Blanchard-Desce	■ CorePartner Institute of Molecular Sciences (ISM, UMR5255)	
■ 2016	■ Oncology	■ 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:

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NEPMIP

NanoEmulsion Platform for Magnetic Particle Imaging

- Sylvie Crauste-Manciet
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2015
- Oncology
- 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.

Publications quoting TRAIL:

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- Data on iron oxide core oil-in-water nanoemulsions for atherosclerosis imaging. Prévot G, Mornet S, Lorenzato C, Kauss T, Gaubert A, Baillet J, Adumeau L, Barthélémy P, Clofent-Sanchez G, Crauste-Manciet S. Data in Brief, 2017;
- Iron oxide core oil-in-water nanoemulsion as tracer for atherosclerosis MPI and MRI imaging Geoffrey Prévota, Tina Kaussa, Cyril Lorenzato, Alexandra Gauberta, Mélusine Larivière, Julie Bailleta, Jeanny Laroche-Traineau, Marie Josée Jacobin-Valat, Laurent Adumeau, Stéphane Mornet, Philippe Barthélémy, Martine Duonor-Cérutti, Gisèle Clofent-Sanchez, Sylvie Crauste-Manciet, International Journal of Pharmaceutics, 2017.

PIAF

PET Imaging of Angiogenesis by 18F-RGD

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

The project will firstly establish the interest of the $\alpha v\beta 3$ 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:

- [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;

Research achievements

- Pd°-catalyzed methyl transfer on nucleosides and oligonucleotides envisaged as a PET tracer E. Fouquet et al. Molecules, 2013, 18, 13654-13665;
- 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.

PRITOR

NeuroPeptide Receptors Imaging for TumOR Targeting

- Elif Hindie
- CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)
- 2013
- Oncology
- 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.

Publications quoting TRAIL:

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- 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., 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;
- 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;
- 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, 2016;
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SUPSIFLU

Supported Silyl Fluorination

- Philippe Hermange
- CorePartner Institute of Molecular Sciences (ISM, UMR5255)
- 2013
- Oncology
- 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:

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TARGLIN

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

- Franck Couillaud
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2015
- Oncology
- 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.

Research achievements

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:

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- PEGylation rate influences peptide-based nanoparticles mediated siRNA delivery in vitro and in vivo. Aldrian G, Vaissière A, Konate K, Seisel Q, Vivès E, Fernandez F, Viguier V, Genevois C, Couillaud F, Démèné H, Aggad D, Covinhes A, Barrère-Lemaire S, Deshayes S & Boisguerin P, Journal of Controlled Release, 2017.

B.15 Workpackage 5 – "Biological bio-imaging markers"

BIOPSYPROSTAPROBE

Antibody-based fluorescence probe for biopsy guidance of prostate cancer

- Franck Couillaud
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2014
- Oncology
- TRAIL funding: 185 000 €

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:

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BRAIN-RESV

Neuroprotective effect of resveratrol in hypoxic ischemic rat pups: how supplementation of the pregnant female could impact brain lesion of the pups?

- Anne-Karine Bouzier-Sore
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2017
- Neurology
- TRAIL funding: 50 000 €

Perinatal hypoxia leads to 1,600 cases of death or strong handicap (50/50%) out of 800,000 births per year in France. Finding ways to prevent or cure such brain diseases is a primary goal of neuroscience research. Reaching it requires an ever-improving understanding of the brain's normal functioning, which is the goal of our InNES project (Investigating Neuronal Energetic Substrate). Moreover, a constant preoccupation of our investigations is to obtain relevant data in order to develop new therapies. Resveratrol (RSV) is a polyphenol present in some plants and diet and has been recently shown to have a neuroprotective effect. In our lab, we also demonstrated that RSV increases significantly glycolysis in the liver. Since brain metabolism, glycolysis and lactate production are of paramount importance in the brain, we propose to study the potential therapeutic role of RSV on hypoxic-ischemic (HI) rat pup brains. The originality of this project will mainly rest on our nutritional and transgenerational approach. RSV will be administered to the pregnant female, near to a nutritional dose, and brain lesions of the 7-day rat pups will be followed in vivo by MRI. In addition, to decipher the mechanisms by which RSV could be neuroprotective, in vitro experiments will be carried out on astrocyte cultures to determine the impact on glial energy metabolism, while rt-qPCR, Western-Blot and immunohistochemistry will be performed rat pup brain samples at specific times post-insult to follow modifications of gene and protein expression. This grant will allow to obtain evidence about the potential benefit of such a therapeutic approach, with, we hope, a clinical trial as our final aim, in collaboration with the Children's Hospital in Bordeaux.

DIFFIR

Ex vivo DIFFusion-weighted MRI of renal Ischemia Reperfusion injury

- Souleymane Maïga
- CorePartner Molecular IMaging and Innovative Therapeutics In Oncology (EA 7435 IMOTION)
- 2017
- Nephrology
- TRAIL funding: 47 000 €

Ischemia-reperfusion injury (IRI) is a sequence that includes organ harvesting, conservation and implantation in the recipient. It plays a key role in the development of early and chronic graft dysfunction. Understanding the effect and mechanisms of physiological adaptation to stress generated by the IRI is one of the most promising research for improving conservation and preservation of grafts. Our previous work on micro-CT already showed that renal IRI, in a preclinical porcine model of renal auto-transplantation, promotes cortical microvascular network remodeling with cortical microvascular rarefaction. The microvascular rarefaction was correlated with a deterioration of renal function, proteinuria and tubular dysfunction, and associated with developing fibrous tissue. Functional MRI allow assessment of multiparametric imaging looking at several pathological changes at once, such as renal vasculature, edema formation, and cellular infiltration. MR diffusion tensor imaging (DTI), with calculation of cortical and medullary fractional anisotropy (FA) provides qualitative and quantitative information about the microstructure of renal tissues. All renal DTI studies have been performed in vivo with a limited spatial resolution and a limited number of encoding directions (6 directions). Ex-vivo imaging allows to apply high spatial resolution parameters and a much higher number of encoding directions, to detect subtle changes of the microstructure, as already shown in the brain. Such a study has never been performed within the kidney. The purposes of this experimental study are to investigate renal microstructural characteristics of normal mouse kidney using DTI parameters obtained with a high resolution ex-vivo DTI technique, to evaluate the consequences of IR on these parameters, in terms of injury and remodeling, in a mouse model of renal IRI and to correlate these changes with histopathological changes and with functional outcome.

Research achievements

GMCOG

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

- Aurélie Ruet
  Thomas Tourdias
- CorePartner "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2016
- Neurology
- 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 processing 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:

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- 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, 2016;
- Hippocampal microstructural damage correlates with memory impairment in clinically isolated syndrome suggestive of multiple sclerosis. Planche V, Ruet A, Coupé P, Lamargue-Hamel D, Deloire M, Pereira B, Manjon JV, Munsch F, Moscufo N, Meier DS, Guttmann CR, Dousset V, Brochet B, Tourdias T. Mult Scler. 2017;
- Microstructural analyses of the posterior cerebellar lobules in relapsing-onset multiple sclerosis and their implication in cognitive impairment. Moroso A, Ruet A, Lamargue-Hamel D, Munsch F, Deloire M, Coupé P, Charré-Morin J, Saubusse A, Ouallet JC, Planche V, Tourdias T, Dousset V, Brochet B. PLoS One. 2017;
- Pattern separation performance is decreased in patients with early multiple sclerosis. Planche V, Ruet A, Charré-Morin J, Deloire M, Brochet B, Tourdias T. Brain Behav. 2017.

IBIONI

Imaging Biomarkers of experimental and clinical neuroinflammation

- Bruno Brochet
- CorePartner "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2012
- Oncology
- 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:

- 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,
- 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, 2015;
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- 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, 2016;
- Hippocampal microstructural damage and memory impairment in clinically isolated syndrome, Planche V at al., MS journal., 2016.

INNES

Investigation on Neuronal Energetic Substrate

- Anne-Karine Bouzier-Sore
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2011
- Neurology
- 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.

Research achievements

Publications quoting TRAIL:

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IPALICA

Inflammatory pathways leading to intracranial aneurysm growth

- Jérome Berge
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2015
- Neurology
- 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.

MEMIM

Multiphoton endomicroscopy for metabolic imaging of macrophages in atherosclerosis

- Gisèle Clofent-Sanchez
- CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)
- 2017
- Cardiology
- TRAIL funding: 50 000 €

Atherosclerosis is a progressive disease that can be regarded as an inflammatory pathology that results from an initial activation of the endothelial cells with further enhancement of oxidative stress, lipid and monocyte recruitment in the arterial wall. The lesions evolve to vulnerable plaques presenting large lipid cores covered by a thin fibrous cap at high risk of rupture and thrombi formation. Despite considerable efforts made to characterize vulnerable plaque, there is still a crucial need for a new imaging tool that allows diagnosis before the pathology suddenly evolved to dramatic events such as stroke and myocardial infarction. Because acute

coronary events depend not only on the severity of luminal narrowing but also on plaque characteristics and inflammation, Imaging must be conducted at the cellular level, target markers of vulnerability and be applied in real-time deeply inside the organism in a minimally invasive manner. Recently, the paradigm of in vivo in situ optical biopsy has been proposed through use of laser-scanning confocal micro-endoscopy. It has been the subject of intense endeavors in the industry (Mauna Kea Technologies, Paris) and also in academic research. However previously reported achievements in micro-endoscopy, in addition of requiring exogenous staining agents (few of them being authorized in the human clinic because of induced toxicity), were limited to non-specific structural and morphological imaging that delivered no information on the metabolism of cells. Recent developments demonstrated by one of the project partner (i.e. XLIM) contribute to change this situation allowing taking advantage of the tremendous potential brought by optical fiber imaging. Otherwise, macrophages play a central role in the pathogenesis of atherosclerosis as the first line of invader cells of the atheroma plaque; in particular, a high level of inflammatory macrophages (also called "M1") is indicative of the plaque progression and the risk of rupture. The premise of the project relies on, for the first time, performing molecular imaging of macrophage phenotypes through an optical fiber for the direct monitoring of several fundamental metabolic processes measured by endogenous biomarkers. Because they are involved in the metabolic pathways within the cell, nicotinamide and flavin adenine dinucleotides (NADH and FAD respectively) represent two fundamentally important metabolic co-factors relevant for the assessment of phenotypes of macrophages. It has been demonstrated that intravital bench-top optical multiphoton microscopy allows the measurement of these two fundamental metabolic markers through their native fluorescences. Moreover, quantitative fluorescence lifetime imaging can help to distinguish between functionally relevant states of NADH (free or bound) and separate contribution of NADPH to the fluorescence signals. The ambition of the project is therefore to demonstrate potentialities of multiphoton microendoscopy for label-free in vivo in situ metabolic imaging of macrophages in their native tissular environment and to apply it to the diagnostic imaging of atherosclerosis.

MIMATHUMAB

Molecular IMaging of ATHeroma with HUMan AntiBody

■ Gisèle Clofent-Sanchez	■ CorePartner Center of Magnetic Resonance of Biological Systems (RMSB, UMR5536)	
■ 2012	■ Cardiology	■ 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.

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;
- 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, 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, 2016;
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SCICOG&REACTIV

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

- Bruno Brochet
- CorePartner "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2011
- Neurology
- 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:

- 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. J Neurol Sci, 2015;
- Deciphering depressive mood in relapsing-remitting and progressive multiple sclerosis and its consequences on quality of life. D Lamargue Hamel, M Deloire, A Ruet, J Charré-Morin, A Saubusse, JC Ouallet, B Brochet. Plos One, 2015;
- Cerebellar assessment in early MS, Moroso A et al., Cerebellum journal, 2016;
- Posterior lobules of the cerebellum and information processing speed at various stages of multiple sclerosis, Moroso A et al., JNNP journal, 2016.

STEAMRI

Whole lung oxygen-enhanced imaging in humains using MRI

■ Gael Dournes	■ CorePartner Bordeaux Cardio-Thoracic Research Center (CRCTB, U1045)	
■ 2016	■ Pneumology	■ 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.

Publications quoting TRAIL:

- Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis: MR Imaging of Airway Mucus Contrasts as a Tool for Diagnosis, Gaël Dournes, MD, PhD, Patrick Berger, MD, PhD, John Refait, Julie Macey, MD, Stephanie Bui, MD, Laurence Delhaes, MD, PhD, Michel Montaudon, MD, PhD, Olivier Corneloup, MD, Jean-François Chateil, MD, PhD, Roger Marthan, MD, PhD, Michaël Fayon, MD, PhD, François Laurent, MD, Thoracic imaging, 2017;
- MRI of the pulmonary parenchyma: Towards clinical applicability ? G. Dournes, J. Maceya, E. Blanchard,P. Bergera, F. Laurent, Pneumologie Clinique, 2017.

TBI

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

■ Jérome Badaut	■ CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)	
■ 2015	■ Neurology	■ TRAIL funding: 250 000 €

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:

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- 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, 2016;
- Vascular impairment as a pathological mechanism underlying long-lasting cognitive dysfunction after pediatric traumatic brain injury. Ichkova A, Rodriguez-Grande B, Bar C, Villega F, Konsman JP, Badaut J. Neurochem Int. 2017.

Research achievements

TRANSFEAR

Translational study of the cerebral substrates involved in pathological fear recovery

- Melissa Bonnet
- CorePartner "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2012
- Neurology
- 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:

- 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, 2015; 78:298–306;
- 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, 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, 2016.

B.16 Workpackage 6 – "Mathematic simulation and modeling"

ARM

Automatic assessment of Radiofrequency ablation Margins

- Baudoin Denis De Senneville
- CorePartner Bordeaux Institute of Mathematics (IMB, UMR5251)
- 2016
- Oncology
- 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.

Publications quoting TRAIL:

- Development of a fluid dynamic model for quantitative contrast-enhanced ultrasound imaging, Baudouin Denis de Senneville, Anthony Novell, Chloé Arthuis, Vanda Mendes, Paul-Armand Dujardin, Frederic Patat, Ayache Bouakaz, Jean-Michel Escoffre, and Franck Perrotin, IEEE Transactions on Medical Imaging, 2017.

DEEP STROKE

DEEP Learning for prediction of long-term motor impairment after STROKE

- Thomas Tourdias
- CorePartner "Physiopathology of neuronal plasticity" Inserm unit (Magendie Institute, U862)
- 2017
- Neurology
- TRAIL funding: 49 924 €

A better and earlier prediction of long-term motor impairment after stroke is strongly needed to improve the treatment of potential disability. Clinical parameters such as patient age and initial stroke severity are already important predictors of motor disability in the long-term. Recently, researchers have identified that detailed

descriptor of the stroke lesion based on early Magnetic Resonance Imaging (MRI) appears to predict some of the long term disability that is not adequately explained by clinical parameters alone. Especially, such MRI prognosis biomarkers are based on more or less direct quantification of the integrity of the corticospinal tract, the main motor pathway. Recent deep learning algorithms for image analysis, especially convolutional neural networks, might provide a relevant and better approach for such prediction that has not been tested yet. Thought out a previously funded project (PHRC) named "Brain Before Stroke" (BBS), the stroke unit and the neuroimaging departments have already enrolled a cohort of 428 ischemic stroke patients for whom they collected clinical parameters and cerebral MRI 24h-to-72h after stroke and at one-year follow-up, in order to identify prognosis markers. The aim of the current project is to explore the potential of deep learning for image analysis applied to the BBS database to improve predictive models of the motor recovery of patients who underwent strokes. More specifically, project team will focus on three consecutive tasks. In task 1, the team will build a model based on deep learning algorithms to automatically segment the stroke lesion in MRI for a faster evaluation of the geometry and location of the lesion. In task 2, the team will develop a model to predict the motor recovery of the patients from MRI taken shortly after stroke. In task 3, we will put the results from task 1 and 2 into perspective by evaluating the potential clinical and industrial transfer of the project.

Publications quoting TRAIL:

- Gait Change Is Associated with Cognitive Outcome after an Acute Ischemic Stroke, Sharmila Sagnier, Pauline Renou, Stéphane Olindo, Sabrina Debruxelles, Mathilde Poli, François Rouanet, Fanny Munsch, Thomas Tourdias, and Igor Sibon, Frontiers in aging neuroscience, 2017;
- Thalamic alterations remote to infarct appear as focal iron accumulation and impact clinical outcome, Gregory Kuchcinski, Fanny Munsch, Renaud Lopes, Antoine Bigourdan, Jason Su, Sharmila Sagnier, Pauline Renou, Jean-Pierre Pruvo, Brian K. Rutt, Vincent Dousset, Igor Sibon and Thomas Tourdias, Brain, 2017.

HETEROMRMAP

MR mapping of renal function heterogeneity to characterize parenchymal nephropathies

■ Benjamin Taton	■ CorePartner Bordeaux Institute of Mathematics (IMB, UMR5251)	
■ 2016	■ Nephrology	■ 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).

MOD

Mathematical modeling of the response to antiangiogenic drugs via medical imaging

■ Thierry Colin	■ CorePartner Bordeaux Institute of Mathematics (IMB, UMR5251)	
■ 2013	■ Oncology	■ 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 Bergonié (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.

Research achievements

Publications quoting TRAIL:

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- 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, 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, 2016;
- Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumour response assessment using RECIST 1.1, F. H. Cornelis, M. Martin, O. Saut, X. Buy, M. Kind, J. Palussiere and T. Colin, European Radiology Experimental, 2017.

NEKOMRI

MRI sequence for bronchial wall segmentation and analysis

■ Fabien Baldacci	■ CorePartner Bordeaux Cardio-Thoracic Research Center (CRCTB, U1045)	
■ 2014	■ Pneumology	■ 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.

Publications quoting TRAIL:

- New methods for the geometrical analysis of tubular organs Grélard, F.; Baldacci, F.; Vialard, A.; and Domenger, J. Medical Image Analysis, 2017.

■ B.17 Workpackage 7 - "Cohort imaging methodology"

ABACI

Automated Brain Anatomy for Cohort Imaging

■ Bernard Mazoyer	■ CorePartner Neurofunctional Imaging Group (GIN, UMR5296)	
■ 2012	■ Neurology	■ 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.

ACTE

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

■ Sandra Chanraud	■ CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)	
■ 2012	■ Neurology	■ 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:

- Compensatory recruitment of neural resources in chronic alcoholism. Chanraud S. and Sullivan EV. Handbook of Clinical Neurology, Vol. 125, 2014;
- Neuroimaging and Alcoholism. Chanraud S, Bernard C. Annales Médico-Psychologiques 2015;
- Brain structural investigation and hippocampal tractography in medication overuse headache: a native space analysis, M. Meyer, G. Di Scala, M. Edde, B. Dilharreguy, F. Radat, M. Allard and S. Chanraud, Behavioral and Brain Functions, 2017.

ADPP

Brain Topology of AD presymptomatic phase

■ Gwenaëlle Catheline	■ CorePartner Aquitaine Institute of Cognitive and Integrative Neurosciences (INCIA, UMR5287)	
■ 2015	■ Neurology	■ 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.

Research achievements

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

Publications quoting TRAIL:

- 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, 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, 2016;
- Patterns of brain atrophy associated with episodic memory and semantic fluency decline in aging, Amandine Pelletier, Charlotte Bernard, Bixente Dilharreguy, Catherine Helmer, Melanie Le Goff, Sandra Chanraud, Jean-François Dartigues, Michèle Allard, Hélène Amieva, Catheline Gwénaëlle, Aging, 2017.

COBRASCAN

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

- François Laurent
- CorePartner Bordeaux Cardio-Thoracic Research Center (CRCTB, U1045)
- 2013
- Pneumology
- 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:

- 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, 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, 2016.

TRAIL&TRACKS

Atlasing whole brain white matter tracts in 300 healthy humans

- Laurent Petit
- CorePartner Neurofunctional Imaging Group (GIN, UMR5296)
- 2011
- Neurology
- 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

B.2 Achievements per Workpackage, presented by Workpackage Coordinators

B.21 Workpackage 1 – "Interventional imaging and MRI guided HIFU" – Coordinator: Bruno Quesson (CRCTB)

Achievements (2011 – 2017): numbers in the text refer to publications in the field listed below

In the context of TRAIL, several research programs have been developed over the last years in the field of interventional MRI (HIFU and radiofrequency ablation), from technological developments and preclinical evaluation, toward 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 (5,6), brain (7), liver (2,7) and muscle (7). 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 (9). 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 (18, 19, 20). 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 (14, 15), thus reducing the risks of damaging surrounding tissue included in the HIFU beam path.

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 (10, 12, 16, 17). Regulatory aspects of the project of treatment of breast cancer have been solved, with the objective to include the first patients in 2018 (international collaboration between Institut Bergonié, INSERM U1045, Image Guided Threapy SA and University of Utah, Pr D Parker). A proof of concept of non-invasive cardiac stimulations with MR guided HIFU has also been published (8) and patented by IHU Liryc, with short terms perspective of tech transfer toward industry.

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 (3). 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 (10). 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 (4).

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 (3). 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 2011-2017, acquisition of devices (HIFU devices and MRI scanners) and research team building from scratch was necessary since the original team working in that field has been closed in 2011. Close collaborations with several industrial partners (Siemens, Image Guided Therapy, IMRicor, Biosense Webster,...) have been created, in order to foster translation of these innovative therapies into clinical reality.

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

1. (*) Pinel K, Genevois C, Debeissat C, Couillaud.F. Imaging of conditional thermo-induced gene silencing in vivo. Scientific Reports, In Press;
2. (*) Bour P, Ozenne V, Marquet F, Senneville BD, Dumont E, Quesson B. Real-time 3D ultrasound based motion tracking for the treatment of mobile organs with MR-guided High Intensity Focused Ultrasound. Int J Hyperthermia, 2018;
3. (*) Sandre O, Genevois C, Garaio E, Adumeau L, Mornet S and Couillaud F. In vivo imaging of local gene expression induced by magnetic hyperthermia. Genes (Basel). 2017; 8(2);
4. (*) Adumeau L., Genevois C., Roudier L., Schatz C, Couillaud F. , Mornet S. Impact of surface grafting density of PEG macromolecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors. Biochim Biophys Acta. 2017;1861(6):1587-1596;
5. (*) 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;
6. (*) 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;
7. (*) 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.;
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11. (*) 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;
12. 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;
13. 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;
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18. 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;
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20. 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.

Research achievements

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 international conferences

More than **70** Communications at international peer-reviewed conferences (ISMRM, ESMRMB, ISTU, FUS Foundation, Heart Rhythm Society, JFR,...)

Scientific awards at international peer-reviewed conferences

1. Ozenne V, Toupin S, Bour P, de Senneville BD, Vaussy A, Lepetit-Coiffé M, Jaïs P, Cochet H, Quesson B. First clinical evaluation of real-time cardiac MR thermometry. International Society of Magnetic Resonance in Medicine 2017, Hawaii, USA. *Summa cum laude* award;
2. 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. ISMRM, Singapour, 2016. *Summa cum laude* award.

Participation to winter and summer schools

- Winter school of Therapeutic Ultrasound – les Houches (2013, 2015 and 2017 - Teaching) international audience;
- OPUS summer school – Lyon (2016 - teaching), international audience;
- Ecole d'imagerie du petit animal appliquée au cancer - Bordeaux (2017 - teaching), national audience.

B.22 Workpackage 2 - "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:

Four research projects were funded in WP2:

- NewFISP in 2012, 250 K€ (PI: S. Miraux)
- HR-DTI in 2012, 130 K€ (PI: B Hiba)
- MDMRI in 2016, 49.6 K€ (PI: B Hiba)
- WhoBoMP2RAGE in 2017, 46 k€ (PI: E Ribot)

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.

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.

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 goal of the project is to develop High Spatial/Angular-resolution DTI for *ex-vivo* validation of tractography.

Five fixed brains were scanned by ultra-high resolution diffusion MRI. First part of the project was dedicated to data post-processing protocols to correct effects of eddy currents, detected in the data during preliminary analyzes. The algorithms originally developed for processing images acquired *in-vivo* in humans have been modified to adapt them to *ex-vivo* data.

Automatic tissue segmentation of white and gray substances has also been established for *ex-vivo* post-processing of data. Diffusion MRI data from the 5 samples were pre-processed. A manual parceling of 120 brain regions has been performed by experts for the first brain and is being performed for a second brain. The tractography of the first brain data, using a multi-tissue multi-shell approach, demonstrated a good performance in comparison with the most advanced methods used until now. An increase in true positives was observed when the multi-shell multi-tissue approach was employed.

› WhoBoMP2RAGE

The "Magnetization-Prepared 2 Rapid Gradient Echo" (MP2RAGE) sequence provides extremely high contrast images and 3-dimensional (3D) T1 relaxation time maps in a very fast and reliable way. This sequence would be an exceptional tool to detect and quantify pathologies affecting several organs of the body, such as metastases.

To apply the MP2RAGE sequence to the abdomen, its Cartesian encoding has been modified by a radial encoding. This largely decreased the sensitivity to respiratory motion of the sequence and resulted in abdominal images with high spatial resolution without movement artifact, without synchronizing the acquisition with the animal's breathing. T1 of hepatic metastases was measured over time, and demonstrated inter and intra-metastasis differences.

In parallel, to accelerate the acquisition of these 3D T1 maps, the "Compressed Sensing" technique was used. Due to the modification of the encoding trajectory, the images were less noisy and 3D T1 maps of mouse brains were obtained in less than 1 minute, while maintaining the T1 values of brain metastases.

■B.23 Workpackage 3 - "DNP" - Coordinator: Eric Thiaudiere (RMSB)

General Objectives of the WP3:

The WP3 aims at developing cutting-edge methods in order to compensate for the intrinsic lack of sensitivity in NMR/MRI experiments.

Two strategies are considered : a) the use of hyperpolarized Nuclei such as 13C (Dissolution DNP) and b) in situ DNP (dynamic nuclear polarization).

a) 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 evaluation of treatments. It is envisioned as well to apply dDNP for investigating brain (neuronal and glial) metabolism.

Research achievements

› 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 micro-dialysis 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 micro-probes 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 pre-clinical and clinical research whole-body systems.

b) In Situ DNP

Coordinator: Pr. Eric Thiaudière, Centre de Résonance Magnétique des Systèmes Biologique - UMR 5536 - CNRS Université de Bordeaux

› Objectives

The goal is to develop 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).

› 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.

› 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.

- in vitro and *ex vivo* proof-of-concept of targeted nitroxide for molecular imaging of elastase.

› In Situ DNP Perspectives

The aim is now to reveal neutrophil elastase activity that occur under acute inflammation such as pancreatitis. *In vivo* experiments need the development of fast and efficient MRI sequences that have to be implemented de novo in a new 0.19T system. A PhD student hired by TRAIL is currently working on this task.

■B.24 Workpackage 4 - "Tracers and constrast agents" - Coordinators: Mireille Blanchard-Desce (ISM), Philippe Fernandez (INCIA)

Objectives of the WP:

The purpose of the Work Package 4 is to develop smart imaging agents in the framework of projects **from bench side 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 and multimodality) or the development of efficient tools to synthesize new molecules or modify biomolecules meant to be used them as tracers and contrast agents. In this framework, projects involving different and complementary imaging modalities (PET, MRI, MPI, NIRF) have been funded. Most approaches involve smart targeting approaches.

The WP4 has actually funded **7 research projects** for a total budget of **654 k€ since 2013**.

› SUPSIFLU (130 k€ since 2013)

aims to develop a new ^{18}F labeling strategy on solid support that may be applicable to a wide range of biological molecules. The ^{18}F fluorination of unsupported bioconjugates synthesized previously (see 2016 report) has been achieved. Good radiochemical yields were obtained. On the other hand, direct fluorination of a resin under study has validated the concept of a "click & label" strategy proposed at the start of the project.

The low yield has yet to be optimized.

This work was the subject of a publication (***T. Cornilleau et al., Bioconjugate Chem. 2017, 28, 2887-2894***) and several communications.

› PRITOR (90 k€ since 2013)

Neuropeptide receptors can be strongly expressed on the surface of tumor cells, offering the possibility, on the one hand, to visualize the extension of these tumors in Positron Emission Tomography (PET) imaging using ^{68}Ga radiolabeled analogues, on the other hand, to treat metastatic patients by internal vectorized radiotherapy using radiolabeled analogues such as ^{177}Lu. A key example has been the development of radiolabeled analogues targeting somatostatin receptors for the imaging and the treatment of neuroendocrine tumors (NETs). We are currently studying the expression of somatostatin receptors in Hodgkin's lymphomas. This diagnostic and therapeutic approach has recently been amplified with the identification of other neuropeptides and their receptors expressed on the surface of tumor cells of different cancers. Another family of neuropeptide receptors appears to be relevant for tumor targeting; bombesin receptors (GRPR and NMBR). Thanks to a close collaboration with the Department of Pathology of the Bergonié Institute (Dr. G. Macgrogan), the expression of GRPR was characterized in more than 1400 primary tumors of breast cancer and metastatic lymph nodes and the correlations between this expression and various clinico-pathological and biological parameters were studied (**Morgat et al, J Nucl Med 2017, 58:1401-1407**).

Another axis concerns the family of neurotensin and neuropeptide-Y receptors. The expression of NTR1 and Y1 in the same bank as for the GRP-R is currently being studied. Finally, other tumors, including prostate cancer, are under study to provide the molecular rational necessary for the development of neurotensin and neuropeptide-Y analogues. Several co-financing were obtained in 2017.

› NEPMIP (35 k€ since 2015)

The objective of the present work was to develop a nanoemulsion platform dedicated for Magnetic Particles Imaging (MPI). Magnetic oil-in-water nanoemulsions (NE) were engineered. These oily droplets were loaded with superparamagnetic iron oxide nanoparticles (SPION) and functionalized with atheroma specific ScFv-Fc TGE4-2C antibody (**Fig 1**). Inclusion of nanoparticles inside NE did not change the hydrodynamic diameter of the oil droplets, close to 180 nm, nor the polydispersity. The droplets were negatively charged (β=−30 mV). *In vitro* MPI signal was assessed by Magnetic Particle Spectroscopy (MPS). NE displayed MRI and MPS signals confirming its potential as new contrast agent. NE MPS signal increase with NPs size close to the gold standard (Resovist) (**Fig.2**). In MRI, NE displayed R2* transversal relaxivity of 45.45, 96.04 and 218.81 mM−1 s−1 for 7, 11 and 18 nm respectively. NE selectively bind atheroma plaque both *in vitro* and *ex vivo* in animal models of atherosclerosis.

Magnetic NE showed reasonable MRI/MPS signals and a significant labelling of the atheroma plaque. These first results support that NE platform could selectively image atherosclerosis and will be followed by *in vivo* experiments in atheroma mice models.

This work was the subject of several publication this year (**G. Prévot et al., International journal of pharmaceutics. 2017, 5;532(2):669-676; G. Prévot et al., Data in brief. 2017, 15;824-827; G. Prévot et al., Data in brief. 2017, 15;876-881**).

Fig 1. Magnetic o/w nanoemulsion functionalized with specific atheroma antibodies (A) SPION nanoemulsion platform concept (B) Transmission Electronic Microscopy image.

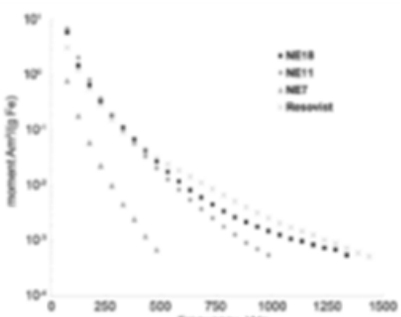


Fig 2. MPS frequency dependence of normalized intensities at 25 mT of nanoemulsions loaded with 7, 11, 18 NPs core SPION

Research achievements

› TARGLIN (150 k€ since 2015)

The objective of the project is to develop peptide-based nanoparticles (PBNs) for addressing siRNAs targeting specific genes in glioblastoma and tumor microenvironment in a mouse xenograft model. *In vivo* imaging is used to determine PBNs bio-distribution, their specific targeting and their role in tumor growth reduction. *In vivo* data are further confirmed up to sub cellular level by histological investigations. Main events and progress in 2017 are the following: As part of the screening program the Montpellier team has synthesized 2 new PBN containing siRNA called W3 and EV3. These new nanoparticles were found highly efficient for firefly luciferase (Fluc) ***in vitro*** inhibition and **have** been assayed *in vivo*. W3-siRNA targeting luciferase has been shown to reduce the bioluminescence signal in U87 subcutaneous tumors in mice. Inhibiting effect was peaking at 24 h after intratumoral injection of W3-siRNA and their inhibiting effect is still detectable at 48 H. An experiment in order to demonstrate W3-siRNA effect on intracerebral U87 tumors is ongoing. However, preparation of very high concentration of W3-siRNA to reduce intracerebral injection volume is a challenging issue. W3-siRNA distribution and cell-penetration has been also investigated in brain tumors. Neurons, glial and endothelial cells were identified by immunohistochemistry using cell-type specific antibodies. The fluorescent-labelled W3-siRNA was found in all different cell-types suggesting no cell-specificity for W3-siRNA nanoparticles. CDK-1 was identified as a potential molecular target for cancer cell. W3-siRNA targeting CDK-1 has been designed and synthesized to be tested in vitro on U87 cells. Efficient inhibition of cell division and proliferation was found *in vitro*. The Inhibiting effect *in vivo* on tumors growth is currently investigated.

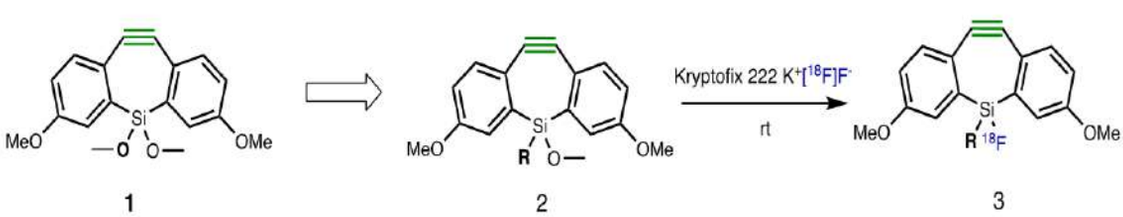
Two publications (**G. Aldrian et al., Journal of controlled release, 2017, 256;79-91; A. Vaissière et al., Journal of nanobiotechnology, 2017, 15; 34**) had been accepted concerning characterization and *in vitro* effect of peptide-siRNA nanoparticles. *In vivo* data have to be completed to reach statistical significance and publication.

› FITTING (49 k€ in 2016)

concerns the synthesis of an ^{18}F-labeled cycloheptyne probe to empower the bioorthogonal ligation technology with PET capabilities for translational applications.

Last year, we successfully synthesized Si-containing molecule **1** (Scheme 1) as a model of bioorthogonal probe for easy introduction of the desired ^{18}F-atom.

Encouraged by the reaction between **1** and modified sugars, the incorporation of a "cold" F-atom (Scheme 1) was developed this year. In order to ensure the stability of the future ^{18}F-labeled probe **3** towards hydrolysis, the importance of the **R group** (Scheme 1) for shielding the central Si-atom was first investigated. As model compounds, Ph_2**R**SiF with **R**=Me, t-Bu and Ph were synthesized and their stability towards hydrolysis was examined by ^{19}F-NMR spectroscopy in D_2O/DMSO and acidic conditions (D_2O/DMSO with AcOH). This study clearly revealed that **t-Bu**Ph_2SiF is a lot more stable than the other two fluorinated compounds. Following this preliminary result, the synthesis of a strained cycloheptyne containing Si-*t*-Bu as central element is currently under development.



Scheme 1. Introduction of 18F-atom on novel bioorthogonal probe

› NANOMULTIMAG (150 k€ in 2016)

proposes a strategy based on biocompatible nanosystems incorporating two complementary contrast agents, i.e., iron oxide nanoparticles (SPIONs) for MRI and MPI imaging and ultra-bright red to NIRF-emitting dyes for both *in vitro* (two-photon fluorescence microscopy) and *in vivo* (FMT) imaging. Yet, different issues have to be addressed to achieve suitable nanosystems for multimodal imaging. These include (i) the labelling with biomarkers specific to the pathology and as little immunogenic as possible, (ii) the use of biocompatible carriers able to vehicle the targeted imaging probes to the micrometric lesions, and (iii) the design of dedicated bright far-red to NIR emitting fluorochromes which maintain fluorescence properties in the multicomponent nanosystem and show large two-photon absorption properties in the NIR1 region.

The targeting issue has been addressed via the engineering of human antibody fragments specifically obtained by *in vivo* phage display technology to recognize over-expressed molecules in the microenvironment of the lesion. Human antibodies specific to biomarkers of the pathology have been characterized, which were reformatted as ScFv-Fc fragments. Furthermore, the "stealth" properties of NE having PEG surface moieties (NE-Peg) have been studied ***in vivo*** (8 mice) by **real time MRI** thanks to its MR contrast agent properties. As a result, stealth and versatile NE (NE Peg-Mal) having maleimide functional groups for further bioconjugation with selected antibody are now available. In addition, biocompatible nanoemulsions loaded with dedicated ultra-bright far-red emitting two-photon fluorophores and strong and magnetic contrast agents (SPION) were designed. They retain both magnetic and fluorescent properties and were phagocytized by macrophages which could then be imaged *in vitro* both by MRI and two-photon fluorescence.

Based on this progress, the next step involves the encapsulation of novel NIRF fluorochromes and SPION into NE-Peg/Peg-Mal and their conjugation with previously selected antibody. The final targeted NE formulation will then be used for post *ex vivo* visualization of micrometric lesions in the mouse animal model of atherosclerosis (two-photon induced fluorescence imaging) chosen for the proof-of-concept of the efficiency of the "nanomultimag" approach - and *in vivo* quantification of the accumulated targeted nanoemulsions (MRI). In parallel, the second approach based on NIR-emitting biocompatible molecular-based nanoparticles (HiFONs) will be implemented. The bioconjugation of these HiFONs is a challenging issue and innovative surface functionalization will be implemented. In addition, incorporation of iron oxide into molecular luminescent nanoparticles will be tested with the aim to provide hybrid nanoparticles for multimodal nanoparticles.

› INNOVATHER (50 k€ in 2017)

is a project to explore the possibilities offered by neuropeptide receptors expressed in breast cancers to develop innovative imaging and therapeutic agents. The originality resides in the target (Y_1 receptor) and efforts made to enhance efficiency of radiopharmaceutical therapy using innovative radionuclides based on an original interdisciplinary approach. The INNOVATHER project deals with organic synthesis, oncology and nuclear medicine fields to obtain results for diagnosis and therapy of some samples of breast cancers (targeted radionuclide therapy is not currently used in breast cancer). Two chemical compounds have been successfully synthetized with high purities. The first compound "pb-12" was specifically designed to be internalized after Y_1-binding (it retains high and selective Y_1-activation potency) and then cleaved into endosomes. The remaining part was chemically modified to be addressed closed to the nucleus. A second compound 'pb-13" is used as negative control (no Y_1-binding) as demonstrated by activation potency experiments. These compounds have been radiolabelled with ^{111}In as surrogate of terbium radionuclides. Radiopharmaceutical characterization is undergoing. Y_1-analogues (pb-12 and pb-13) are under evaluation for affinity on breast cancer cells using PWR technology (CBMN, Dr I. Alves). The next step will be to labelled with native terbium pb-12 and pb-13 and then use the proton beam of the AIFIRA plat-form (CENBG, access granted in June 2018) to perform intracellular X spectroscopy of native terbium. This mapping of terbium localization will be fused to electronic microscopy data obtained with the "Pole d'Imagerie Electronique" of Bordeaux University. This will be the first intracellular imaging data of terbium. Other innovative radionuclides might be considered for similar applications in future projects.

Research achievements

■B.25 Workpackage 5 – "Biological bio-imaging markers" – Coordinator: Gisèle Clofent-Sanchez (RMSB)

Objectives of the WP:

The general objective of WP5 is to develop **efficient targeting and imaging of biomarkers** in order to **predict and follow the course of pathologies and provide personalized treatments**.

The thirteen funded WP5 projects have covered Neurology, Oncology, Bronchial and Cardio-Vascular diseases. All the projects relied on different approaches such as **metabolomic and proteomic** for the discovery of new biomarkers, **molecular imaging** of biomarkers that can be directly visualized *in vivo* (molecular imaging of lactate in INNES project; grey matter alteration in GM-COG project…) or targeted by means of functionalized nano-objects (Antibody-based probes for prostatic carcinoma or atherosclerosis in BIOPSYPROSTAPROBE or MIMATHUMAB projects), **development of novel multimodal imaging modalities** both useful for diagnosis and therapy. Each project fosters the development of a multidisciplinary approach with a will to translate research from bench to bedside. Learning from physiological processes, cellular or molecular events occurring in pathologies is the stepping stone to implement *ad hoc* bio-imaging modalities in humans, predict disease progression and evaluate therapeutic intervention.

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 1 month with anxiety as revealed by DTI. Longterm evaluation has been conducted at 6, 12 and 18 months with acquisition of the DTI and PWI changes associated with behavioral evaluation. *Ex-vivo* vascular reactivity was studied in the neurovascular coupling after CHILD©. MRI structural changes on the brain structures and cognitive outcomes will be evaluated in soccer players after sub-concussive impacts, compared to 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. This project highlights the importance of following cerebral perfusion as a new biomarker in parallel to the behavioural evaluation.

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:

1-By performing qPCR analyses on auto-immune encephalomyelitis (EAE) mice, results were obtained acknowledging the role of complement in the pathological cross-talk between glial cells and hippocampal dendrites with consequences in memory deficit. Data are collected to prove that pharmacologically inhibiting the complement protects against the dendritic loss induced by MS and forward against memory disorders. Advanced *in vivo* diffusion imaging using diffusion tensor imaging (DTI) and NODDI (Neurite Orientation Dispersion and Density Imaging) was optimized to decipher the microstructure of hippocampal subfields.

2-From data collected in persons with clinically isolated syndrome (CIS) suggestive of MS, it was found that Gray matter microstructural alterations precede deep gray matter volume loss. The cognitive disorders present at the early stage of the disease could be partially explained by these morphological and functional brain modifications.

3- Alterations in phenotype and cytokine expression profile of circulating T lymphocytes called circulating T follicular helper (cTfh) have been observed in patients with different forms of MS compared to 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- Projects "Imaging Biomarkers of experimental and clinical neuroinflammation" IBIO-NI; and "Imaging Biomarkers of brain gray and white matter in multiple sclerosis cognitive impairment" SCICOG&REACTIV

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.

The SCI-COG program studies the correlations between cognitive disorders and markers of brain disconnection in MR imaging. The REACTIV program studies the cognitive rehabilitation in Multiple Sclerosis and assessment by neuroimaging.

(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. Segmentation analyses were performed on human MRI data in order to obtain the volumes of several sub-cortical regions, particularly concerning both amygdala structures. A correlation was observed between right amygdala volume and rostro-prefrontal activation during extinction. This correlation could predict fear relapse in healthy human subjects.

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.

Research achievements

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 in a neonate rat model.

Current scientific activities and results:

Results clearly show a neuroprotective effect of lactate treatment 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, rather than through the signal molecule pathway, via the GPR81 receptor. Analyses on metabolism and molecular targeting of lactate are done using NMR HR-MAS spectroscopy and 7T MRI *in vivo* imaging. Behavioral tests have been developed to confirm the neuroprotection, in the long term, on animals having undergone HI. The most spectacular results are obtained for animals having received a triple lactate injection. These results are the proof that astrocyte lactate is an essential neuronal substrate.

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.

6-Project "Neuroprotective effect of resveratrol in hypoxic-ischemic rat pups: how supplementation of the pregnant female could impact brain lesion of the pups". BrainRsv

PI: Anne-Karine Bouzier-Sore

Perinatal hypoxia leads to 1,600 cases of death or strong handicap (50/50%) out of 800,000 births per year in France. Finding ways to prevent or cure such brain diseases is a primary goal of neuroscience research.

Current scientific activities and results:

The team demonstrated that RSV increases significantly glycolysis in the liver. Since brain metabolism, glycolysis and lactate production are of paramount importance in the brain, the project aims to study the potential therapeutic role of Resveratrol (RSV), a polyphenol present in some plants on hypoxic-ischemic (HI) rat pup brains. Preliminary results obtained by diffusion MRI highlight the neuroprotective effect of transgenerational administration of RSV. To decipher the mechanisms by which RSV could be neuroprotective, *in vitro* experiments will be carried out on astrocyte cultures to determine the impact on glial energy metabolism, while rt-qPCR, Western-Blot and immunohistochemistry will be performed rat pup brain samples at specific times post-insult to follow modifications of gene and protein expression.

Relevance with WP5 TRAIL funding:

This grant will allow to obtain evidence about the potential benefit of such a therapeutic approach, with an expected clinical trial, in collaboration with the Children's Hospital in Bordeaux.

Biomarkers in Nephrology

Project "*Ex vivo* DIFFusion-weighted MRI of renal Ischemia Reperfusion injury". DIFFIR

PI: Souleymane Maïga

Ischemia-reperfusion injury (IRI) is a sequence that includes organ harvesting, conservation and implantation in the recipient. It plays a key role in the development of early and chronic graft dysfunction. Understanding the effect and mechanisms of physiological adaptation to stress generated by the IRI is one of the most promising research for improving conservation and preservation of grafts.

Current scientific activities and results:

A high resolution *ex-vivo* DTI (MR diffusion tensor imaging) technique is proposed to investigate renal microstructural characteristics of normal mouse kidney. Then, DTI will be applied *in vivo* in a mouse model of renal IRI to evaluate its sensitivity before to propose specific protocols to humans.

Relevance with WP5 TRAIL funding:

This study is an experimental preclinical research, necessary for a precise characterization of renal microstructural changes after IRI and remodeling, the objective being to improve renal graft dysfunction and graft loss in humans.

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. Cancer detection includes imaging and tumor biomarker dosage like PSA (prostate-specific antigen), but actually all of examinations cannot diagnose PCa 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 imaging methods for biopsy guidance are required for early detection that can greatly enhance life expectancy.

Current scientific activities and results:

BIOPSYPROSTAPROBE project was dedicated to the development of both (1) a dual modalities imaging setup combining echography and fluorescence tomography and (2) a specific imaging probe for imaging prostate cancer based on a high affinity anti-PSMA antibody scFv (single chain antibody fragment) fragment. The technologic part of the project, which is to enrich ultrasound imaging currently used in clinic with fluorescence tomography information, is currently on going and funded par Région Aquitaine. Two endorectal hybrid imaging probes have been ordered to VERMON for translational studies on human samples and later on patients. Specific *in vivo* targeting of prostate cancer was demonstrated by injecting an anti-PSMA scFv fragment, labeled with a near-infrared fluorophore, to an orthotopic model of prostate cancer.

Relevance with WP5 TRAIL funding:

NIR-labeled anti-PSMA scFv has been developed as a clinical probe for hybrid imaging-guided targeted biopsies, combining echography and fluorescent tomography. A functionalized nanovector specific to prostate cancer will be designed to establish in vivo on mice orthotopic model the proof of concept of its effectiveness for diagnosis, for specific internalization in cancer cells and for drug specific targeting.

Biomarkers in bronchial diseases

Project STEAMRI
PI: Gaël 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 0_2- enhancement study is thus between 6 and 10 minutes, versus 30 minutes initially.

The study combines a feasibility study of 10 healthy volunteers and a population of 15 patients with constrictive bronchiolitis in patients with bone marrow transplants. The project is promoted by the CHU of Bordeaux and submitted to this body. To date, agreements with institutional partners are underway to submit the project to the Committee for the Protection of Persons. Due to the use of an inhaled contrast agent, the study is indeed classified as type 1 in the new Jardé law, which therefore requires a notice and a declaration with the "Agence Nationale de Sécurité du Médicament".

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

IPALICA project the project focuses on mechanisms involved in the growth and rupture of intracranial aneurysms. The objective is to better understand the aneurysm pathophysiology in order to identify potential biomarkers of aneurysm instability reflecting the rupture risk and to identify potential therapeutic targets. This study is based on the multi-modality analysis (transcriptomics, proteomics, metabolomics and immune-histology) of aneurysm walls taken surgically and intra-aneurysmal blood samples taken during endovascular treatment.

Current scientific activities and results:

Thanks to the two teams of neurosurgery, more than 40 human walls of cerebral aneurysms were harvested and used for transcriptomic and metabolomic analyzes as well as 30 intra-aneurysmal blood samples, allowing a proteomic analysis focused on inflammation.

Different transcriptomic profiles and upregulated inflammatory pathways in aneuvrysm walls compared to normal cortical arteries and in ruptured aneurysm compared to unruptured aneurysm walls were identified. Higher levels of inflammatory proteins (cytokines – chemokines – growth factors) were found in intra-aneurysmal sampling compared to femoral sampling and different proteomic profiles were identified between intra-aneurysmal sampling of ruptured and unruptured aneurysms. A correlation between transcriptomic data (gene expression) from the aneuvrysm wall and proteomic data from intra-aneurysmal sampling (cytokines concentration) suggests that there are intra-aneurysmal blood markers of inflammation of the aneurysm wall. HRMAS NMR-based analysis of human cerebral aneurysm walls reveals different metabolomic profiles between ruptured and unruptured aneurysm walls (higher concentration of taurine and lower concentration of choline in ruptured versus unruptured aneurysm walls).

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 βIIbβ3 integrin (TEG4) for its relevance to detect high-risk atheroma plaques rich in platelets. Antibody fragments (scFv) were used to functionalize original NPs, designed for multimodal imaging (MRI, near infra-red fluorescence (NIRF)) in a regio-selective way to preserve their activity. Moreover, when multiple copies of scFv fragments were grafted to nanoparticles, kinetics of binding as assessed by SPR analyses showed a gradual increase in avidity. Taking advantage of the bimodality, both MRI and NIRF were performed in an animal model of the pathology (ApoE-/- mice). A quantification method was set up for targeted NPs detection and proves their value as a potential diagnosis agent.

- A high-throughput flow cytometry assay on rabbit protein extracts was implemented to identify hundreds of scFv candidates issuing from several rounds of *in vivo* phage display selection in a rabbit model of atherosclerosis (collaboration with LFB Biotechnologies). The specificity of these 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.

-Another way to identify candidates from *in vivo* phage display selection was set up with the development of an

in silico approach using third generation single-molecule real-time (SMRT) sequencing with the (PacBio) RS II platform in collaboration with the firm Pacific Biosciences. This collaborative work has allowed for the sequencing of millions of full-length scFv reads.

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.

3- Project "Multiphoton endomicroscopy for metabolic imaging of macrophages in atherosclerosis" MEMIM
PI: Gisèle Clofent-Sanchez

Atherosclerosis is a progressive disease that can be regarded as an inflammatory pathology where macrophages play a central role as the first line of invader cells of the atheroma plaque. In particular, a high level of inflammatory macrophages (also called "M1") is indicative of the plaque progression and the risk of rupture. The premise of the project relies on, for the first time, performing molecular imaging of macrophage phenotypes through an optical fiber for the direct monitoring of energetic metabolism states (glycolysis and oxidative phosphorylation) measured *in vivo* by ratios of NADH and FAD endogenous biomarkers. Specific M1/M2 macrophage metabolic signatures obtained with proper NADH/FAD ratio may thus decipher clinical M1 versus M2 phenotypes.

Current scientific activities and results:

The human pro-monocytic cell line THP-1 was differentiated in macrophages with PMA and further activated with LPS and IFNβ to obtain M1 macrophages or IL4+IL13 to obtain M2 macrophages. The M1 and M2 phenotypes were properly evaluated with a battery of antibodies recognizing robust biomarkers able to distinguish M1 (such as CD197) and M2 (such as CD206) phenotypes using flow cytometry. The measured autofluorescence of the metabolic co-factors NADH and FAD showed differences in NADH between M1 and M2 phenotypes. However a clear M2 phenotype is difficult to obtain with the THP-1 cell line, justifying the use of MDM (Monocyte-derived Macrophages). Clear M1 and M2 phenotypes were obtained. Autofluorescence images will soon be acquired through the purchase of a portable incubator that will allow the proper delivery of MDM to the XLIM laboratory in Limoges after polarization and phenotyping in CRMSB in Bordeaux. Indeed, the interindividual differences of the primary cells necessitate that the analysis of the phenotypes and the autofluorescence are made on the same cells.

Relevance with WP5 TRAIL funding:

The concept of macrophage optical imaging is highly relevant towards atherosclerosis assessment. The developed microendoscope technologies focused on metabolic imaging are clearly innovative and have the potential to bring new insight into biological studies and clinical diagnostic of atherosclerosis.

Research achievements

B.26 Workpackage 6 – "Mathematic simulation and modeling" – Coordinator: Pierrick Coupé (LaBRI)

Objectives:

The workpackage (WP6) "Mathematical simulation and modelling" is devoted to the development of innovative mathematical modelling and image processing methods to automatically extract and analyze relevant information from medical images. Based on last advances in computer vision and machine learning, this WP aims at proposing new computer-aided diagnosis and prognosis tools dedicated to clinicians. WP6 is highly connected to WP2, WP5 and WP7 and an important number of researchers are jointly involved in these WP. Over the past years, the projects that have been developed in TRAIL focused on several applications in oncology, in nephrology, pneumology and neurology.

› Automatic assessment of Radiofrequency Ablation Margins (ARM):

The aim of this project was 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. To this end, a new multi-modal deformable registration method has been proposed. The registration has been designed to cope with complex 3D deformations such as the one that the liver may undergo.

› MOD

The aim of this project was to propose patient-specific simulation of tumor growth, to analyze response to the treatment. To this end, new biomarkers that were built on mathematical models and parametrized thanks to multimodal images have been developed. This project lead to the software NENUPHAR and the creation of a spin-off.

› NEKOMRI

This project aimed at developing a new segmentation tools for the bronchial tree. The project lead to an industrial transfer with Intrasens.

› DEEP STROKE

This project is based on a partnership between the neuroimaging department of Bordeaux University Hospital and the start-up DESKi in order to create new tools based on Deep Learning to help patients suffering from cerebral infarction. The developed tool automatically enables to segment cerebral infarction on diffusion imaging, thus directly provides information on the volume and location of the lesion to the clinician.

› HeteroMRMap

This 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 image data.

In addition to these TRAIL projects, other co-funded projects with IdEx and the Cluster CPU have been supported by TRAIL. The first one deals with abnormality detection using sparse-based modeling of brain anatomy for early detection of 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 Workpackage 7 – "Cohort imaging methodology" – Coordinator: François Laurent (CRCTB)

The main objectives of WP7 are:

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.

› 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.

› ACTE

is a morphofunctional evaluation of corticocerebellar circuits implicated in cognitive brain and functional connectivity. In 2017, one TRAIL-quoting paper has been published and one scientific presentation of results has been performed abroad (San Francisco, USA). Academic collaboration has been developed in order to implements tools for analyzing functional connectivity in aging brain and a thesis on the subject is ongoing.

› ADPP

The 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. In 2017, two papers have been published and two presentations have been performed at scientific events.

During the second year of the ongoing PhD, two major goals were reached: i) Analyze of the relationship between episodic memory decline and functional connectivity of the posterior DMN in aging subjects. A manuscript on these results is currently being written to be submitted to an international journal ; ii) Development of the pipeline allowing analyzes of structural connectivity and preliminary statistical description of these data before the multimodal analysis which will be conducted during the third year.

› 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.

The year 2017 was mainly dedicated to the recruitment of two cohorts (BCPO Grenoble and Nancy). A new study ACQUA-VIP was initiated, exploitation of results has begun and will likely be done in 2018. A complementary study to a 2016 Thorax publication that partially uses COBRA data is currently has been submitted.

› TRAILS&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

Research achievements

B.3 Scientific communication

B.31 Publications quoting TRAIL

a) 126 publications have been published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP1 - MR Guided HIFU and interventional imaging	MRGHIFU	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
		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
		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
		2017	Combination of principal component analysis and optical-flow motion compensation for improved cardiac MR thermometry, S Toupin , B Denis de Senneville, V Ozenne, P Bour, M Lepetit-Coiffe, M Boissenin, P Jais and B Quesson, Physics in Medicine & Biology, jan 2017	Physics in Medicine & Biology
		2017	Feasibility of real-time MR thermal dose mapping for predicting radiofrequency ablation outcome in the myocardium in vivo, Solenn Toupin , Pierre Bour, Matthieu Lepetit-Coiffé, Valéry Ozenne, Baudouin Denis de Senneville, Rainer Schneider, Alexis Vaussy, Arnaud Chaumeil, Hubert Cochet, Frédéric Sacher, Pierre Jaïs, and Bruno Quesson, Journal of Cardiovascular Magnetic Resonance, Feb 2017	Journal of Cardiovascular Magnetic Resonance
		2017	Impact of surface grafting density of PEG macromolecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors, Laurent Adumeau, Coralie Genevois, Lydia Roudier, Christophe Schatz, Franck Couillaud, Stephane Mornet, BBA - General Subjects, Feb 2017	BBA general subjects
		2017	Real-Time Monitoring of Tissue Displacement and Temperature Changes during MR-Guided High Intensity Focused Ultrasound, Pierre Bour, Fabrice Marquet, Valery Ozenne, Solenn Toupin, Erik Dumont, Jean-Francois Aubry, Matthieu Lepetit-Coiffe, and Bruno Quesson, Magnetic Resonance in Medicine, Jan 2017	Magnetic Resonance in Medicine
WP2 - New sequence and new contrast	HRDTI	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

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP2 - New sequence and new contrast	HRDTI	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
		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	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	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
		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
		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	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	VolBrain: An Online MRI Brain Volumetry System, José V.Manjón and Pierrick Coupé, Frontiers in Neuroinformatics, July 2016	Frontiers in Neuroinformatics

Research achievements

publications published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP2 - New sequence and new contrast	HRDTI	2017	CERES: A new cerebellum lobule segmentation method, Jose Romero, Pierrick Coupe, Remi Giraud, Vinh-Thong Ta, Vladimir Fonov, Min Tae Park, Mallar Chakravarty, Aristotle Voineskos, Jose Manjon, NeuroImage, Jan 2017	NeuroImage
		2017	HIPS: A new hippocampus subfield segmentation method, Jose E. Romero, Pierrick Coupe, Jose V. Manjon, Neuroimage, nov 2017	NeuroImage
		2017	Towards a Unified Analysis of Brain Maturation and Aging across the Entire Lifespan: A MRI Analysis, Pierrick Coupé, Gwenaelle Catheline, Enrique Lanuza, and Jose Vicente Manjon, Human Brain Mapping, july 2017	Human Brain Mapping
		2017	SuperPatchMatch: An Algorithm for Robust Correspondences Using Superpixel Patches, Rémi Giraud, Vinh-Thong Ta, Aurélie Bugeau, Pierrick Coupé, and Nicolas Papadakis, IEEE, july 2017	IEEE TRANSACTIONS ON IMAGE PROCESSING
	NEWFISP	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
		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
		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	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
		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

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP2 - New sequence and new contrast	NEWFISP	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
		2017	In vivo MEMRI characterization of brain metastases using a 3D LookLocker T1-mapping sequence, Charles R. Castets, Néha Koonjoo, Andreea Hertanu, PierreVoisin, Jean-Michel Franconi, Sylvain Miraux & Emeline J. Ribot, Nature Scientific Reports, jan 2017	Nature Scientific Reports
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
		2017	Online 1HβMRS measurements of timeβvarying lactate production in an animal model of glioma during administration of an antiβtumoral drug, Yannick Crémillieux, Roberto Salvati, Ursule Dumont, Noël Pinaud, Véronique Bouchaud, Stéphane Sanchez, Stefan Glöggler, Alan Wong, NMR in Biomedicine, oct 2017	NMR in Biomedicine
		2017	Orotracheal manganese-enhanced MRI (MEMRI): An effective approach for lung tumor detection Andrea Bianchi, Oliviero L. Gobbo, Sandrine Dufort, Lucie Sancey, François Lux, Olivier Tillement, Jean-Luc Coll, Yannick Crémillieux, NMR in Biomedicine, sept 2017	NMR in Biomedicine
	TRAILDNP	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
		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
		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
		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
	FITTING	2017	Aquaporins through the brain in health and disease: From water to gas movements, Friscourt F, Badaut J, J Neuro Res. August 2017	Journal of Neurosciences Research

Research achievements

publications published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
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
	NANOMULTI-MAG	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
		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
	NEPMIP	2017	Data on atherosclerosis specific antibody conjugation to nanoemulsions. Prévot G, Duonor-Cérutti M, Larivière M,Laroche-Traineau J, Jacobin-Valat MJ Barthélémy P Clofent-Sanchez G, Crauste-Manciet S. Data in Brief, 2017	Data in brief
		2017	Data on iron oxide core oil-in-water nanoemulsions for atherosclerosis imaging. Prévot G, Mornet S, Lorenzato C, Kauss T, Gaubert A, Baillet J, Adumeau L, Barthélémy P, Clofent-Sanchez G, Crauste-Manciet S. Data in Brief, 2017	Data in brief
		2017	Iron oxide core oil-in-water nanoemulsion as tracer for atherosclerosis MPI and MRI imaging Geoffrey Prévota, Tina Kaussa, Cyril Lorenzato, Alexandra Gauberta, Mélusine Larivière, Julie Bailleta, Jeanny Laroche-Traineau, Marie Josée Jacobin-Valat, Laurent Adumeau, Stéphane Mornet, Philippe Barthélémy, Martine Duonor-Cérutti, Gisèle Clofent-Sanchez, Sylvie Crauste-Manciet, International Journal of Pharmaceutics, oct 2017	International Journal of Pharmaceutics
	PIAF	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
		2013	Pd°-catalyzed methyl transfer on nucleosides and oligonucleotides envisaged as a PET tracer E. Fouquet et al. Molecules, 2013, 18, 13654-13665.	Molecules
		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
	PRITOR	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

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP4 - Tracers and contrast agents	PRITOR	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
		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.
		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	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	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	European journal of nuclear medicine and molecular imaging
		2017	Expression of Gastrin-Releasing Peptide Receptor in Breast Cancer and Its Association with Pathologic, Biologic, and Clinical Parameters: A Study of 1,432 Primary Tumors, Clément Morgat, Gaétan Mac-Grogan, Véronique Brouste, Valérie Vélasco, Nicolas Sévenet, Hervé Bonnefoi, Philippe Fernandez, Marc Debled, and Elif Hindié, Journal of Nuclear Medicine, oct 2017	journal of nuclear medicine
	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
		2017	Last-Step Pd-Mediated [11C]CO Labeling of a Moxestrol-Conjugated o-Iodobenzyl Alcohol: From Model Experiments to in Vivo Positron Emission Tomography Studies, Thomas Cornilleau, Mette Simonsen, Maylou Vang, Nada Taib-Maamar, Jean Dessolin, Hélène Audrain, Philippe Hermange, and Eric Fouquet, Bioconjugate Chemistry, nov 2017	Bioconjugate Chemistry
	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
		2017	A retro-inverso cell-penetrating peptide for siRNA delivery. Vaissière A, Aldrian G, Konate K, Lindberg MF, Jourdan C, Telmar A, Seisel Q, Fernandez F, Viguier V, Genevois C, Couillaud F, Boisguerin P & Deshayes S Journal of Nanobiotechnology, May 2017	Journal of Nanobiotechnology
		2017	PEGylation rate influences peptide-based nanoparticles mediated siRNA delivery in vitro and in vivo. Aldrian G, Vaissière A, Konate K, Seisel Q, Vivès E, Fernandez F, Viguier V, Genevois C, Couillaud F, Démèné H, Aggad D, Covinhes A, Barrère-Lemaire S, Deshayes S & Boisguerin P, Journal of Controlled Release, April 2017	Journal of Controlled Release

Research achievements

publications published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
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
		2017	In Vivo Imaging of Local Gene Expression Induced by Magnetic Hyperthermia, Olivier Sandre, Coralie Genevois, Eneko Garaio, Laurent Adumeau, Stéphane Mornet, and Franck Couillaud, Genes, Feb 2017	Genes
		2017	In vivo imaging of prostate cancer tumors and metastasis using non-specific fluorescent nanoparticles in mice. Coralie Genevois, Arnault Hocquelet, Claire Mazzocco, Emilie Rustique, Franck Couillaud, and Nicolas Grenier. Int. J. Mol. Sci. 2017	Int. J. Mol. Sci
	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	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
		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
		2017	Hippocampal microstructural damage correlates with memory impairment in clinically isolated syndrome suggestive of multiple sclerosis. Planche V, Ruet A, Coupé P, Lamargue-Hamel D, Deloire M, Pereira B, Manjon JV, Munsch F, Moscufo N, Meier DS, Guttmann CR, Dousset V, Brochet B, Tourdias T. Mult Scler. nov 2017	MS journal
		2017	Microstructural analyses of the posterior cerebellar lobules in relapsing-onset multiple sclerosis and their implication in cognitive impairment. Moroso A, Ruet A, Lamargue-Hamel D, Munsch F, Deloire M, Coupé P, Charré-Morin J, Saubusse A, Ouallet JC, Planche V, Tourdias T, Dousset V, Brochet B. PLoS One. nov 2017	PLoS One
		2017	Pattern separation performance is decreased in patients with early multiple sclerosis. Planche V, Ruet A, Charré-Morin J, Deloire M, Brochet B, Tourdias T. Brain Behav. Jun 2017	Brain Behavior
	IBIONI	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
		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
		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

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP5 - Biological bioimaging markers	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	Hippocampal microstructural damage and memory impairment in clinically isolated syndrome, Planche V at al., MS journal., oct 2016	MS journal
	INNES	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
		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
		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	Analytical method
		2017	A neuronal MCT2 knockdown in the rat somatosensory cortex reduces both the NMR lactate signal and the BOLD response during whisker stimulation. Mazuel, L., Blanc, J., LRepond, C., Bouchard, V., Raffard G., Déglon, N., Bonvento, G., Pellerin, L., and Bouzier-Sore A.-K. PlosOne, April 2017	Plos One
		2017	Current Technical Approaches to Brain Energy Metabolism, Barros LF, Bolaños JP, Bonvento G, Bouzier-Sore AK, Brown A, Hirrlinger J, Kasparov S, Kirchhoff F, Murphy AN, Pellerin L, Robinson MB, Weber B, Glia, oct 2017	Glia

Research achievements

publications published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP5 - Biological bioimaging markers	MIMATHUMAB	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
		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
		2017	PacBio sequencing and IMGT/HighV-QUEST analysis of full-length scFv from an in vivo selected phagedisplay combinatorial library, Audrey Hemadou, Véronique Giudicelli, Melissa L. Smith, Marie-Paule Lefranc, Patrice Duroux, Sofia Kossida, Cheryl Heiner, Lance Helper, John Kuijpers, Alexis Groppi, Jonas Korlach, Philippe Mondon, Florence Ottones, Marie-Josée Jacobin-Valat, Jeanny Laroche-Traineau, Gisèle Clofent-Sanchez, Frontiers in Immunology, déc 2017	Frontiers in Immunology
	SCICOG & REACTIV	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
		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
	STEAMRI	2017	Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis: MR Imaging of Airway Mucus Contrasts as a Tool for Diagnosis, Gaël Dournes, MD, PhD, Patrick Berger, MD, PhD, John Refait, Julie Macey, MD, Stephanie Bui, MD, Laurence Delhaes, MD, PhD, Michel Montaudon, MD, PhD, Olivier Corneloup, MD, Jean-François Chateil, MD, PhD, Roger Marthan, MD, PhD, Michaël Fayon, MD, PhD, François Laurent, MD, Thoracic imaging, April 2017	Journal of Thoracic Imaging
		2017	MRI of the pulmonary parenchyma: Towards clinical applicability ? G. Dournes, J. Maceya, E. Blanchard,P. Bergera, F. Laurent, Pneumologie Clinique, Feb 2017	Pneumologie Clinique
	TBI	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

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
		2017	Vascular impairment as a pathological mechanism underlying long-lasting cognitive dysfunction after pediatric traumatic brain injury. Ichkova A, Rodriguez-Grande B, Bar C, Villega F, Konsman JP, Badaut J. Neurochem Int. Apr 2017	Neurochem Int
	TRANSFEAR	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
		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
	PUBLICATION FROM THE COMMUNITY	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	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	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
		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
		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
WP6 - Mathematical simulation and modeling	ARM	2017	Development of a fluid dynamic model for quantitative contrast-enhanced ultrasound imaging, Baudouin Denis de Senneville, Anthony Novell, Chloé Arthuis, Vanda Mendes, Paul-Armand Dujardin, Frederic Patat, Ayache Bouakaz, Jean-Michel Escoffre, and Franck Perrotin, IEEE Transactions on Medical Imaging, August 2017	IEEE Transactions on Medical Imaging
	DEEPSTROKE	2017	Gait Change Is Associated with Cognitive Outcome after an Acute Ischemic Stroke, Sharmila Sagnier, Pauline Renou, Stéphane Olindo, Sabrina Debruxelles, Mathilde Poli, François Rouanet, Fanny Munsch, Thomas Tourdias, and Igor Sibon, Frontiers in aging neuroscience, nov 2017	Frontiers in Aging Neuroscience

Research achievements

publications published over the 2011-2017 period:

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP6 - Mathematical simulation and modeling	DEEPSTROKE	2017	Thalamic alterations remote to infarct appear as focal iron accumulation and impact clinical outcome, Gregory Kuchcinski, Fanny Munsch, Renaud Lopes, Antoine Bigourdan, Jason Su, Sharmila Sagnier, Pauline Renou, Jean-Pierre Pruvo, Brian K. Rutt, Vincent Dousset, Igor Sibon and Thomas Tourdias, Brain, nov 2017	Brain
	MOD	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
		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
		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
		2017	Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumour response assessment using RECIST 1.1, F. H. Cornelis, M. Martin, O. Saut, X. Buy, M. Kind, J. Palussiere and T. Colin, European Radiology Experimental, nov 2017	European Radiology Experimental
	NEKOMRI	2017	New methods for the geometrical analysis of tubular organs Grélard, F.; Baldacci, F.; Vialard, A.; and Domenger, J. Medical Image Analysis, nov 2017	J. Medical Image Analysis
WP7 - Cohort Imaging Methodology	ACTE	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
		2015	Neuroimaging and Alcoholism. Chanraud S, Bernard C. Annales Médico-Psychologiques 2015	Annales Médico-Psychologiques
		2017	Brain structural investigation and hippocampal tractography in medication overuse headache: a native space analysis, M. Meyer, G. Di Scala, M. Edde, B. Dilharreguy, F. Radat, M. Allard and S. Chanraud, Behavioral and Brain Functions, April 2017	Behavioral aand brain function
	ADPP	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
		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

WP	TRAIL PROJECT	YEAR	TRAIL QUOTED PUBLICATION	JOURNAL
WP7 - Cohort Imaging Methodology	ADPP	2017	Patterns of brain atrophy associated with episodic memory and semantic fluency decline in aging, Amandine Pelletier, Charlotte Bernard, Bixente Dilharreguy, Catherine Helmer, Melanie Le Goff, Sandra Chanraud, JeanβFrançois Dartigues, Michèle Allard, Hélène Amieva, Catheline Gwénaëlle, Aging, May 2017	Aging
	COBRASCAN	2015	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	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	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.32 Scientific communications during international events

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	HIFU	23rd Congress Shanghai	Alteration of the blood brain barrier induced by HIFU	2013	Shanghai	China
		Leloir Institute	Alteration of the blood brain barrier induced by HIFU	2013	Buenos Aires	Argentina
		Oxford University	Alteration of the blood brain barrier induced by HIFU	2013	Oxford	UK
	MRGHIFU	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.	2014	Chicago	USA
	MRGHIFU	Congrès international ESMRMB	Toupin S, Ozenne V, Bour P, Quesson B, De Senneville BD. A robust PCA-based motion estimation approach for MR Thermometry radiofrequency ablation monitoring.	2015	Edinburgh	UK
	MRGHIFU	Congrès international 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
	MRGHIFU	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
	MRGHIFU	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

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	MRGHIFU	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
		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
		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
		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
		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	Washing-ton	USA
		COST radiomag meeting	Couillaud F. Hyperthermia of tumor microenvironment for therapeutic purposes.	2016	Athens	Greece
		COST radiomag meeting	Couillaud F. Odyssey of nanoparticles from the tube to the tumor cells. How to bring bricks together?	2016	London	UK
		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	Singapore	Singapore
		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	Singapore	Singapore
		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	Singapore	Singapore
		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	Singapore	Singapore
		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.	2016	Tel Aviv	Israel
		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

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
1	MRGHIFU	20th International conference of the Society for Cardiac Magnetic Resonance	B Quesson, ICMR EP Instrumentation or devices (conférence invitée)	2017	Washing-ton	USA
		20th International conference of the Society for Cardiac Magnetic Resonance	B Quesson, real-time MRI cardiac Electrophysiology: Disease targets and device progress. (conférence invitée)	2017	Washing-ton	USA
		38th Heart rhythm Society (HRS)	Ozenne V, Toupin S, Bour P, de Senneville BD, Vaussy A, Lepetit-Coiffé M, Jaïs P, Cochet H, Quesson B. First clinical evaluation of real-time cardiac MR thermometry.	2017	Chicago	USA
		European COST Radiomag	Sandre O, Genevois C, Garaio E, Adumeau L, Mornet S & Couillaud F. In Vivo Imaging of Local Gene Expression Induced by Magnetic Hyperthermia. Réseau	2017	Bilbao	Spain
		European Focused Ultrasound Symposium (EUFUS)	Bour P, Ozenne V, Marquet F, Denis de Senneville B, Dumont E and Quesson B. 3D ultrasound based motion tracking with MR-thermometry.	2017	Leipzig	Germany
		International Society of Magnetic Resonance in Medicine 2017	Ozenne V, Toupin S, Bour P, de Senneville BD, Vaussy A, Lepetit-Coiffé M, Jaïs P, Cochet H, Quesson B. First clinical evaluation of real-time cardiac MR thermometry. (Summa cum laude award)	2017	Hawaii	USA
		International Society of Magnetic Resonance in Medicine 2017	Toupin S, Ozenne V, Bour P, Schneider R, Lepetit-Coiffé M de Senneville BD Dumont E, Jaïs P, Quesson B. Active Catheter Tracking for Cardiac MR Thermometry During Radiofrequency Ablation.	2017	Hawaii	USA
2	HRDTI	20th annual meeting of Human Brain Mapping	Impact of DWI denoising on Track-Density Imaging. Coupe P, Periot O, Manjon J, Hiba B, Allard5 M.	2014	Hamburg	Germany
	NEWFISP	ISMRM 2015	5 oral communications or posters	2015	Toronto	Canada
		ESMI	T1 Longitudinal quantification of iron-oxyde particles using a 3D UTE Spiral Look-Locker sequence at 7T	2016	Utrecht	The Nether-lands
		ISMRM 2016	3D Longitudinal MRI Studies on Novel Tissue-Engineered Bone Constructs in Living Rats: Volume & Perfusion Assessments	2016	Singapore	Singapore
		ISMRM 2016	4D Flow MRI of the Cardiovascular System in Small Animals at 7T with an Ultrashort TE Sequence Combined with an Injection of Iron Nanoparticle	2016	Singapore	Singapore
3	ON-COFLUX	ISMRM	MR Spectroscopy of very small volumes (< 0.4 µl) of 13C-labelled metabolites using microcoil detection: application to online measurements of cerebral microdialysate	2014	Toronto	Canada
		EUROMAR meeting	Online monitoring of brain metabolites: A microdialysis and microcoil approach, CMR meeting	2015	Prague	Czech Republic

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
3	ON-COFLUX	ISMRM meeting	MR Spectroscopy of very small volumes (< 0.4 µl) of 13C-labelled metabolites using microcoil detection: application to online measurements of cerebral microdialysate.	2015	Toronto	Canada
		Asia-Pacific EPR Symposium	Elodie Parzy (oral communication), In vivo Mapping of Protease Activity using Overhauser-enhanced MRI: Challenges and Promises	2016	Irkurtsk	Russia
		European Molecular Imaging Meeting. Utrecht	Simultaneous MRI and MRS spectrocopy of small volume (1 microlitre) intracerebral metabolites: a combined microdialysis and microcoil application	2016	Utrecht	The Nether-lands
		ISMRM 2016	Simultaneous imaging and 1H spectroscopy of small volume (1 µl) intracerebral microdialysate in healthy and glioblastoma-bearing rats using highly sensitive micro-coils.	2016	Singapore	Singapore
		ESMRMB	Online MRS measurement of extracellular lactate concentration during administration of anti-tumoral drugs in an animal model of glioma	2017	Barcelona	Spain
		International Symposium on Metabolic and redox interactions between neurons and astrocytes in health and disease	Online NMR profiling of subnanomole quantities of metabolites in brain dialysate.	2017	Salamanca	Spain
		ISMRM	135. Quantification of lactate concentration in micro-dialysate during cerebral activation using 1H-MRS and sensitive NMR microcoil	2017	Hawaii	USA
	TRAILDNP	ENIM	In vivo OMRI of proteolysis.	2014	Antwerp	Belgium
		ISMRM	In vivo OMRI of proteolysis.	2014	Milan	Italy
		ISMRM Merit AWARD ISMRM 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
		ISMRM 2016	A combined microcoil and microdialysis approach to measure metabolic response in real-time.	2016	Singapore	Singapore
4	BRAIN-RESV	ESMRMB	Maternal supplementation with resveratrol and/or ethanol in hypoxic ischemic injury in rat neonates par Roumes, H. Mazuel, L. Dumont, U. Daher, B. Sanchez, S. Blanc, J. Bouchaud, V. Chateil, J. F. Beauvieux, M.–C. Bouzier–Sore, A.K.	2017	Barcelona	Spain
	FITTING	5th European Chemical Biology Symposium	F. Friscourt – Talk – A turn-on bioorthogonal probe for the visualization of biomolecules in no-wash conditions	2017	Budapest	Hungary
		5th European Chemical Biology Symposium	Z. Chinoy – Poster - Novel Glycan-Reporters for Metabolic Oligosaccharide Engineering – Awarded Best Poster Prize	2017	Budapest	Hungary

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
4	FITTING	Symposium on Molecular Architectures for Fluorescent imaging of Cells	C. Favre – Poster - Sydnones Reporters for Enhanced Fluorogenic Bioorthogonal Ligations	2017	Karlsruhe	Germany
		Symposium on Molecular Architectures for Fluorescent imaging of Cells	F. Friscourt – Talk - The Sweet Imaging of Living Cells	2017	Karlsruhe	Germany
	IMME-LAPT	COST Thematic Workshop "Bio-inspired Nanotechnologies for Biosensing"	Aptamers, clever oligonucleotides for bio-sensing	2013	Sitges	Spain
		NanobioEurope	NanobioEurope	2013	Toulouse	France
		Tohoku University	International Symposium, Tohoku University	2013	Sendai	Japan
	INNES	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
		EWCBR 2016	Lactate: more than a neuronal energetic subtrate. by Bouzier–Sore A. K. (conférencier invité)	2016	Villars-sur-Ollon	Switzer-land
		ESMRMB	Study of the variations in lactate levels during in vivo whisker stimulation BY Functional MRI and localized 1H MRS: comparative study between control and shMCT2 rats par Blanc, J. Jollé, C. Mazuel, L. Roumes, H. Deglon, N. Bonvento, G. Pellerin, L. Bouzier–Sore, A. K.	2017	Barcelona	Spain
		International Symposium on Metabolic and redox interactions between neurons and astrocytes in health and disease	AAV2/DJ–miR30E–shMCT2: Promising tool to specifically knockdown MCT2 expression in neurons and investigate its role in neuroenergetics. par Jollé, C., C. Pythoud, N. Déglon, A.K. Bouzier–Sore, and L. Pellerin.	2017	Salamanca	Spain
		International Symposium on Metabolic and redox interactions between neurons and astrocytes in health and disease	Lactate: more than a neuronal energetic substrate: an NMR approach. Bouzier–Sore	2017	Salamanca	Spain

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
4	INNES	International Symposium on Metabolic and redox interactions between neurons and astrocytes in health and disease	Study of variation in lactate levels during in vivo whisker stimulation by functional MRI and localized 1H MRS: comparative study between control and shMCT2 rats par Blanc, J. Jollé, C. Mazuel, L. Roumes, H. Déglon, N. Bonvento, G. Pellerin, L. Bouzier–Sore, A. K.	2017	Salamanca	Spain
		XIII European Meeting on Glial Cells in Health and Disease - Euroglia	Lactate: more than a neuronal energetic substrate: a NMR approach par Bouzier–Sore	2017	Edinburgh	UK
	NANO-MULTI-MAG	Antibody Tech, 2017. Monash University	Enrichment of antibodies issued from in vivo phage display assessed by in silico and in vitro assays: potential ligands for atheroma imaging	2017	Prato	Italy
		5th Symposium on βPhospholipids in Pharmaceutical Research	PEGylated phospholipids nanoemulsions for in vivo imaging of subcutaneous tumors	2017	Heidelberg	Germany
		12th European Molecular Imaging Meeting – EMIM 2017	PEGylated phospholipids nanoemulsions for in vivo imaging of subcutaneous tumors	2017	Cologne	Germany
	NEPMIP	Euskampus	Formulation of nanoobjects for Magnetic Particles Imaging	2015	San Sebastian	Spain
		5th Symposium on βPhospholipids in Pharmaceutical Research,	PEGylated phospholipids nanoemulsions for in vivo imaging of subcutaneous tumors	2017	Heidelberg	Germany
		12th European Molecular Imaging Meeting – EMIM 2017	MPI/MRI/fluorescence multimodal imaging nanoemulsion platform	2017	Cologne	Germany
	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	Gothenburg	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 (oral).	2014	Gothenburg	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	Gothenburg	Sweden
		Theranostics world congress Ga-68 and PRRT	Development of a 68Ga-ranatensin analog for bombesin receptor PET molecular imaging (oral communication)	2015	Baltimore	USA

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
4	PRITOR	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
		Annual Meeting of the European Association of Nuclear Medicine	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	Barcelona	Spain
		Annual 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
		Annual Congress of the European Association of Nuclear Medicine	Neurotensin receptor-1 expression in human prostate cancer and lymph nodes metastases	2017	Vienna	Austria
		Society of Nuclear Medicine and Molecular Imaging	Expression of Gastrin-releasing Peptide Receptor in, Breast Cancer and Its Association with Pathologic, Biologic, and Clinical Parameters: A Study of 1432 Primary Tumors	2017	Denver	USA
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
		Réseau European COST Radiomag, Avril 2017	Adumeau L, Genevois C, Roudier L, Schatz C, Couillaud F & Mornet S. Impact of surface grafting density of PEG macro-molecules on dually fluorescent silica nanoparticles used for the in vivo imaging of subcutaneous tumors.	2017	Bilbao	Spain
	GMCOG	10th annual meeting of the FENS	Membrane dynamics of AQP4: a new key pathway for physiopathological brain cell communication?	2016	Copenha-gen	Denmark
		24th annual meeting of the ISMRM	Thalamus Optimized Multi-Atlas Segmentation at 3T	2016	Singapore	Singapore
		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)	Cognitive impairment in primary progressive multiple sclerosis	2016	New York	USA

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
5	GMCOG	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
		International meeting on cognition in multiple sclerosis (IMSCOGS)	Social cognition and cognitive impairment in multiple sclerosis	2016	New York	USA
		EAN	Pattern separation performance is decreased in patients with early multiple sclerosis	2017	Amsterdam	Nether-lands
		ESMRMB	High resolution NODDI and DTI to highlight hippocampal alterations induced by experimental multiple sclerosis	2017	Barcelona	Spain
		RSNA	High resolution imaging and beyond	2017	Chicago	USA
		XIII European meeting on glial cells in health and disease	Imaging and pathophysiology of early memory impairment in multiple sclerosis.	2017	Edinburgh	UK
	IBIONI	ECTRIMS ACTRIMS	Including ecological assessment in cognitive screening in MS D Hamel	2014	Boston	USA
		IMSCOGS	Ecological assessment in cognitive screening in MS B Brochet	2014	Barcelona	Spain
		ECTRIMS	"Hippocampal microstructural damage and memory impairment in clinically isolated syndrome". V. Planche	2015	Barcelona	Spain
		ECTRIMS	"Vulnerability of dentate gyrus to microglial activation leads to early memory impairment in a model of multiple sclerosis." V. Planche	2015	Barcelona	Spain
		ECTRIMS	Cerebellar sub-structures in cognitive impairment: Volumetric And Microstructural Analyses At Different Stages Of Multiple Sclerosis. A Moroso.	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
	INNES	Euroglia	Organisation of a symposium "Astrocyte network contribution in neuroimaging signals" and conference "Functional neuro-energetic and brain imaging: how do astrocytes contribute to the signal?"	2013	Berlin	Germany
		Gordon conférence	Gordon conference, poster	2013	Ventura	USA
		Université Lausanne	NMR spectroscopy "for dummies" and its application to decipher metabolism. Conférence invitée.	2014	Lausanne	Switzer-land
		ISMRM	Towards MRS using High–Resolution Magic–Angle Coil Spinning: application to brain metabolism.	2014	Milan	Italy
		ESMRMB	Early neuroprotective effect of lactate in neonatal hypoxic ischemic brain damages.	2015	Edinburgh	UK
		Euroglia	Neonatal hypoxic ischemic brain damages: early neuroprotective effect of lactate.	2015	Bilbao	Spain

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
5	INNES	Gordon Conference	Early neuroprotective effect of lactate in neonatal hypoxic ischemic brain damages.	2015	Ventura	USA
		ISMRM	MR Spectroscopy of very small volumes of 13C-labelled metabolites using microcoil detection: application to online measurements of cerebral microdialysate.	2015	Toronto	Canada
	IPALICA	Meeting aneurysm patho-physiopathology	IPALICA	2017	Kyoto	Japan
	MIMA-THUMAB	10th International Conference on the Scientific and Clinical Applications of Magnetic Carrier	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
		Conferences in the Baker Heart and Diabetes Institute	Theranostic of atherosclerosis using human antibody-targeted multi-modal nanoparticles for in situ delivery of drugs	2015	Melbourne	Australia
		Euskampus 2015	Multi-modal nanoparticles for atherosclerosis imaging	2015	San Sebastian	Spain
		PEGS Europe Protein & Antibody Engineering Summit	A high-throughput method based on flow cytometry for the screening of phage-scFvs for the theranostic of atherosclerosis	2015	Lisbon	Portugal
		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	Thailand
		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	Thailand
		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	Lisbon	Portugal
		Antibody Tech, Monash University	Enrichment of antibodies issued from in vivo phage display assessed by in silico and in vitro assays: potential ligands for atheroma imaging	2017	Prato	Italie
		ESMRMB 34th Annual Scientific Meeting	Targeted multimodal nanoparticles for molecular imaging in a mouse model of atherosclerosis	2017	Barcelona	Spain
	STEAMRI	Congrès européen de radiologie	MRI of airways	2017	Vienna	Austria
	TBI	Gordon Research Conference	CNS Barrier Function in Juvenile Traumatic Brain Injury	2016	New London, NH	USA

Research achievements

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
5	TBI	Brain 2017	Acute gliovascular phenotype depends on primary injury severity in a new juvenile Closed Head Injury with Longterm Disorders (CHILD) model par B. Rodriguez-Grande, A. Obenaus, A. Ichkova, T. Bessy, J. Aussudre, E.Barse, B. Hibba, G. Catheline, G. Barriere and J. Badaut (oral communication)	2017	Berlin	Germany
		Brain 2017	Vascular reactivity changes of the intracortical blood vessels after juvenile traumatic brain injury par A. Ichkova, B. Rodriguez-Grande and J. Badaut (poster)	2017	Berlin	Germany
		SFN 2017	Intracorical blood-vessel and MRI alterations after juvenile closed head injury par J. Badaut, A. Ichkova, G. Coutrand, S. S. Bertrand, B. Rodriguez-Grande, A. Obenaus (oral communication)	2017	Washington	USA
		National Neurotrauma Symposium 2017	Acute gliovascular phenotype depends on primary injury severity in a new juvenile Closed Head Injury with Longterm Disorders (CHILD) model par B. Rodriguez-Grande, A. Obenaus, A. Ichkova, T. Bessy, J. Aussudre, E.Barse, B. Hibba, G. Catheline, G. Barriere and J. Badaut (poster)	2017	Snowbird, UT	USA
		National Neurotrauma Symposium 2017	"Dawn of a New Day: Brain Edema is 'Back in the Game' with New Discoveries!" Badaut-Obenaus Water Channels and Brain Edema: Success and Failure Badaut	2017	Snowbird. UT, USA	USA
6	MOD	Cancer seminar, UAB	Imagerie et Cancer (Th. Colin)	2017	Birmingham	USA
		Waves 2017	Imagerie, modélisation et Cancer (Th. Colin)	2017	Athens	USA
	NEKOMRI	CAIP 2015	Precise cross-section estimation on tubular organs	2015	Valetta	Malta
		ESTI 2015	Lung morphology assessment of cystic fibrosis using MRI with ultrashort echo time at submillimeter spatial resolution	2015	Barcelona	Spain
		RSNA 2015	Lung morphology assessment of cystic fibrosis using non-contrast enhanced proton MRI with submillimeter details at 1.5 Tesla	2015	Chicago	USA
7	ACTE	Donders Discussions.	Motor control in aging: Sensori-motor network connectivity at rest and motor performance -Dupuy M.	2015	Nijmegen	The-Netherlands
		EFIC 8th International 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. October 2013	2015	Firenze	Italy
		Cognitive Neuroscience Society Congress	Age-related differences in time course of brain activation and connectivity during feedback-based associative learning.	2016	San Francisco	USA
		Human Brain Mapping	Age-related differences in time course of brain activation and connectivity during associative learning.	2016	Geneva	Switzerland
		Cognitive Neurosciences	Age-related differences in time course of brain connectivity during associative learning.	2017	San Francisco	USA

WP	TRAIL PROJECT	EVENT	SCIENTIFIC COMMUNICATION	YEAR	CITY	COUNTRY
7	COBRAS-CAN	European Society of Thoracic Imaging	G. Dournes, F. Coste, C. Dromer, F. Baldacci, F. Picard, M. Montaudon, R. Marthan, P. Berger, F. Laurent. CT measurement of small vessels as a tool to phenotype COPD subjects with severe pulmonary hypertension.	2014	Amsterdam	The Nether-lands
	TRAIL & TRACKS	ISMRM Scientific Workshop	Hau J, Sarubbo S, Petit L, Stem-based tractography of long association fibers of the human brain. In: ISMRM Scientific Workshop - Diffusion as a Probe of Neural Tissue Microstructure.	2013	Podstrana	Croatia
		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.	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	2014	Hamburg	Germany
		Conférence au Brain Imaging and Analysis Center (BIAC)	Petit L, Stem-based approach to study the anatomical connectivity of human brain white matter pathways. The inferior fronto-occipital fasciculus.	2014	Durham	USA
		Conférence au Laboratoire d'Imagerie de la Connectivité de Sherbrooke (SCIL)	Hau J Mapping whole brain white matter tracts in 410 healthy humans.	2014	Sherbrooke	Canada
		23rd Annual Meeting of the International Society of Magnetic Resonance in Medicine (ISMRM)	Poster : Recognition of bundles in healthy and severely diseased brains" by Garyfallidis E, Côté M-A, Hau J, Perchey G, Petit L, Cunnanne SC, Descoteaux M	2015	Toronto	Canada

Research achievements

B.4 Patents and Software Protection Agency recordings

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.

"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.

"A specific binding molecule directed against galectin-3 protein."
Publication date: 05/10/2017
Inventors: Gisèle Clofent-Sanchez

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.

SOFTWARE PROTECTION AGENCY RECORDINGS

"Muppet"
IDDN.FR.001.220007.000.S.P.2015.000.31230

"Meta_poumon"
IDDN.FR.001.220006.000.S.P.2015.000.31230

"CADMOS"
IDDN.FR.001.220005.000.S.P.2015.000.10600

"Segmentit: Antepedia Deposit"
215-12-03-10-27-36

C/ Scientific animation and training

C.1 Conferences

TRAIL teams invited 41 international speakers to give lectures in Bordeaux:

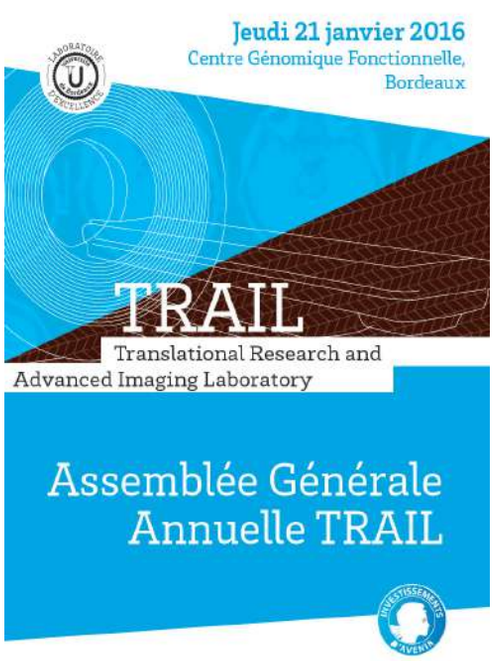
DATE	SPEAKER	ORGANIZATION	LECTURE
November 2012	Dr Pr Marco Essig	Heidelberg University, Germany	Anticipating medical imaging research evolutions
April 2013	Dr Ernesto SANZ-ARIGITA	CITA Alzheimer, San Sebastian, Spain	Multidimensional biomarkers for early detection of neurodegeneration
July 2013	Professor Jeff W.M. BULTE	The Johns Hopkins University School of Medicine, Baltimore, USA	Seeing Cells with MRI
	Professor Martin MEYER	Department of Psychology, Plasticity and Learning in the healthy aging brain, University of Zurich, Switzerland	Time, speech, and the right hemisphere
November 2013	Professor Yasutaka FUSHIMI	Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Japan	Cooperation between Kyoto University and Toshiba Medical
September 2013	Dr Wafaa ZARAOUI	University of Marseille, France	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, Paris, France	Evaluating tumor vascular structure and its response to therapy with pre-clinical contrast-enhanced ultrasound
	Pr Mike MODO	University of Pittsburgh, USA	Image-guided injection and non-invasive monitoring of tissue engineering in stroke
	Pr Constantin COUSSIOS	BUBBL, Oxford University, United Kingdom	Real-time passive acoustic mapping of tissue ablation and drug delivery by ultrasound
	Pr Sébastien LECOMMANDOUX	University of Bordeaux, France	Biomimetic polymersomes, a promising platform towards personalized nanomedicine
January 2014	Pr Dennis PARKER	Utah Center for Advanced Imaging Research, Salt Lake City, USA	MRI Guided Focused Ultrasound of the Breast
May 2014	Pr Brian RUTT	Stanford School of Medicine, USA	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, Australia	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	University of Salamanca, Spain	Molecular bases of the metabolic programs of neurons and astrocytes
April 2015	Pr Juan P. BOLANOS	University of Salamanca, Spain	Astrocytes boost neuronal protection during glutamatergic neurotransmission
May 2015	Pr Yukio MIKI	Osaka City University, Japan	Imaging of the pituary
	Pr Juan P. BOLANOS	University of Salamanca, Spain	Mitochondrial respiratory chain assembly dictates differential ROS production in neurons and astrocytes
July 2015	Dr Stanislas RAPACCHI	University of California, Los Angeles, USA	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, Japan	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, USA	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, France	Le scanner spectral à comptage photonique
February 2016	Dr Anatol KONTUSH	INSERM Research Unit 1166, University Pierre and Marie Curie, Paris, France	Nanoparticules pour le théranostic de l'athérosclérose
June 2016	Pr OBENAUS	Loma Linda University, USA	Long-term Neuroimaging of Human Neural Stem Cells following Neonatal Hypoxic-Ischemic Injury
	Associate Pr Simon ESKILDSEN	Aarhus University, Denmark	Capillary dysfunction in Alzheimer's disease
September 2016	Associate Pr Nicolas FARRUGIA	University of Brest, France	Spatio temporal dynamics of functional connectivity extracted using dictionary learning approaches
October 2016	Dr. Florence DELMAS	Bruker	PET/MRI multimodal imaging: unparalleled accuracy

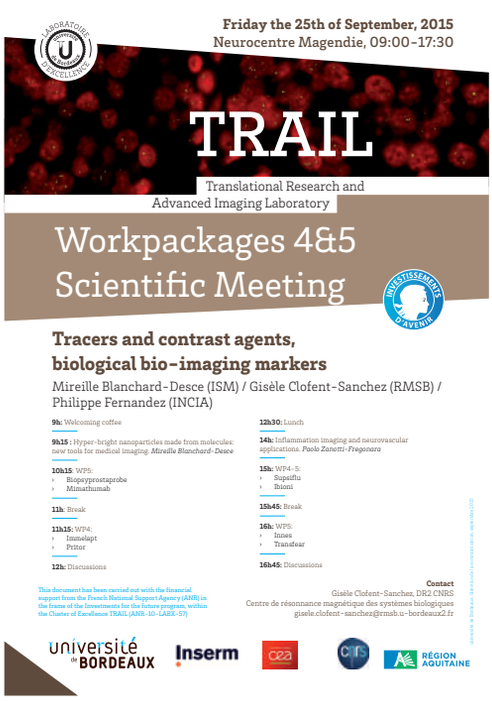
DATE	SPEAKER	ORGANIZATION	LECTURE
November 2016	Pr Lorenz HIRT	Unil-CHUV, Lausanne, Switzerland	Non invasive biomarkers in the ischemic mouse brain
	Dr Joao DUARTE	Laboratoire d'imagerie du métabolisme, Lausanne, Switzerland	Alterations of brain metabolism in type 2 diabetes: a magnetic resonance study in vivo
	Pr Luc PELLERIN	Unil-CHUV, Lausanne, Switzerland	Bolstering neuroenergetics as a neuroprotective strategy
February 2017	Pr Banafshe LARIJANI	Ikerbasque	Oncoprotein activation and dynamics in cancer: a new vision of cancer diagnostics
June 2017	Pr Bertrand TAVITIAN	Charité, Berlin, Germany	Retinal imaging in neurology-current research and clinical applications
	Pr Friedemann PAUL	MR Solutions	New TEP/MRI developments not using cryogenic liquids
July 2017	Fabrice CHAUMARD	INSERM U970 & Hôpital Européen Georges-Pompidou, Paris, France	Exploration du lien entre métabolisme et vascularisation par imagerie

C.2 General assemblies

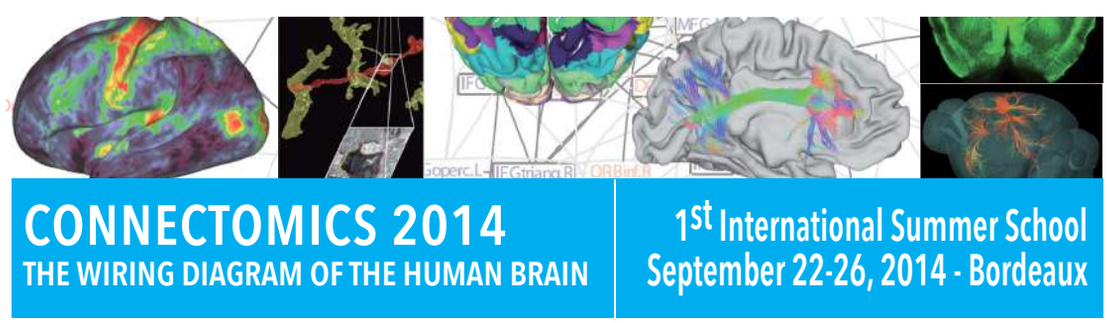


Scientific animation and training

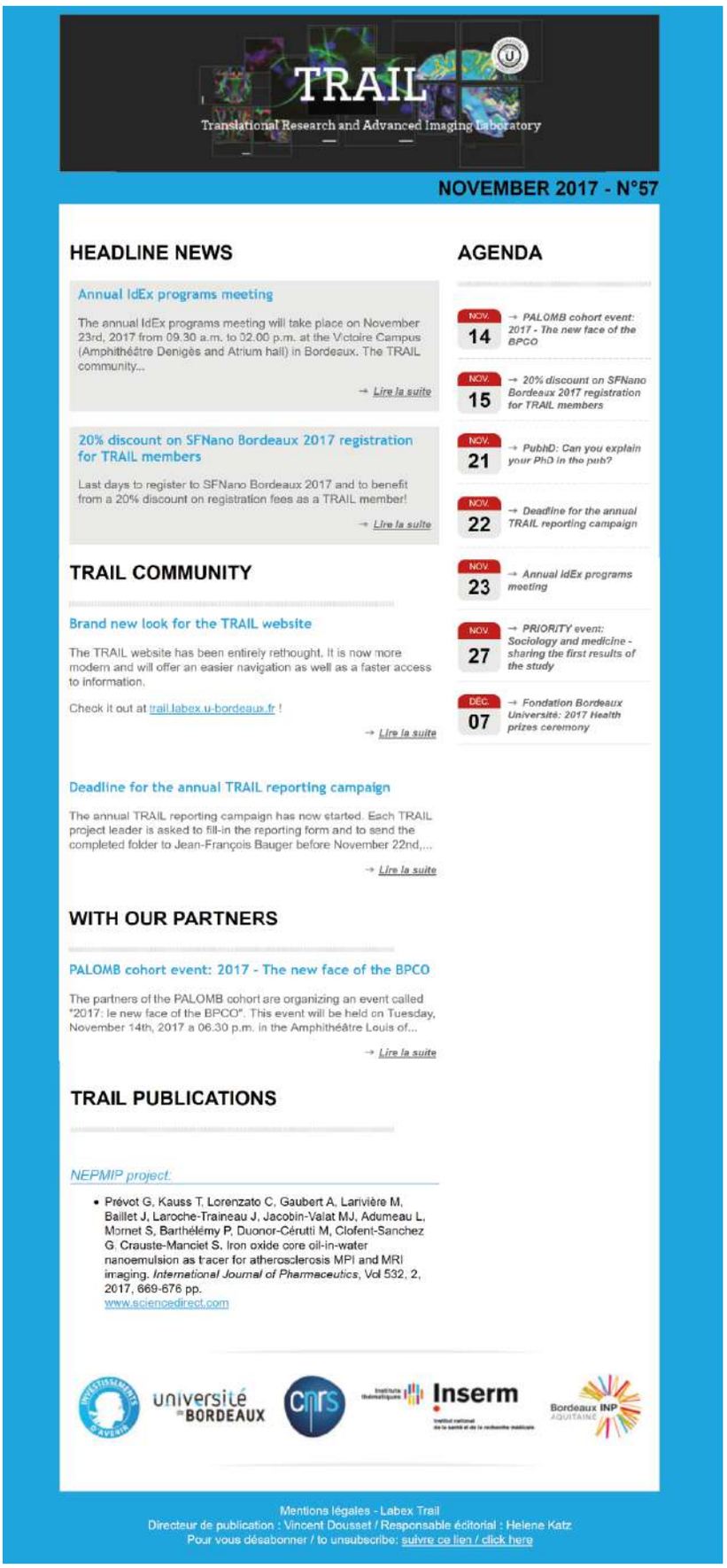
C.3 Scientific days



C.4 Summerschools



C.5 Informing the Community



TRAIL

Translational Research and Advanced Imaging Laboratory

NOVEMBER 2017 - N°57

HEADLINE NEWS

Annual IdEx programs meeting

The annual IdEx programs meeting will take place on November 23rd, 2017 from 09.30 a.m. to 02.00 p.m. at the Victoire Campus (Amphithéâtre Denigès and Atrium hall) in Bordeaux. The TRAIL community...

→ Lire la suite

20% discount on SFNano Bordeaux 2017 registration for TRAIL members

Last days to register to SFNano Bordeaux 2017 and to benefit from a 20% discount on registration fees as a TRAIL member!

→ Lire la suite

TRAIL COMMUNITY

Brand new look for the TRAIL website

The TRAIL website has been entirely rethought. It is now more modern and will offer an easier navigation as well as a faster access to information.

Check it out at trail.labex.u-bordeaux.fr !

→ Lire la suite

Deadline for the annual TRAIL reporting campaign

The annual TRAIL reporting campaign has now started. Each TRAIL project leader is asked to fill-in the reporting form and to send the completed folder to Jean-François Bauger before November 22nd,...

→ Lire la suite

WITH OUR PARTNERS

PALOMB cohort event: 2017 - The new face of the BPCO

The partners of the PALOMB cohort are organizing an event called "2017: le new face of the BPCO". This event will be held on Tuesday, November 14th, 2017 a 06.30 p.m. in the Amphithéâtre Louis of...

→ Lire la suite

TRAIL PUBLICATIONS

NEPMIP project:

- Prévot G, Kauss T, Lorenzato C, Gaubert A, Larivière M, Baillet J, Laroche-Traineau J, Jacobin-Valat MJ, Adumeau L, Mornet S, Barthélémy P, Duonor-Cérutti M, Clofent-Sanchez G, Crauste-Manciet S. Iron oxide core oil-in-water nanoemulsion as tracer for atherosclerosis MPI and MRI imaging. *International Journal of Pharmaceutics*, Vol 532, 2, 2017, 669-676 pp.
www.sciencedirect.com

AGENDA

NOV. 14 → *PALOMB cohort event: 2017 - The new face of the BPCO*

NOV. 15 → *20% discount on SFNano Bordeaux 2017 registration for TRAIL members*

NOV. 21 → *PubhD: Can you explain your PhD in the pub?*

NOV. 22 → *Deadline for the annual TRAIL reporting campaign*

NOV. 23 → *Annual IdEx programs meeting*

NOV. 27 → *PRIORITY event: Sociology and medicine - sharing the first results of the study*

DÉC. 07 → *Fondation Bordeaux Université: 2017 Health prizes ceremony*

Mentions légales - Labex Trail
Directeur de publication : Vincent Dousset / Responsable éditorial : Helene Katz
Pour vous désabonner / to unsubscribe: suivre ce lien / click here

D/ Attractiveness

D.1 International academic partnerships

WP	APPLIED MEDICAL AREA	TRAIL PROJECT	INTERNATIONAL COLLABORATION
1	Cardiology	MRGHIFU	- NIH (Mickael Hansen): open source image reconstruction software (2015)
			- University of Utah: performing hardware and sequence adaptation for different MRI scanner
2	Cardiology	NEWFISP	- University of Mons: contrast agents development for preclinical cardio imaging
			- University of Wisconsin: algorithms for 4D angiography
	Neurology	HRDTI	- Universidad de Valencia: extending HR-DTI method for q-ball and high b-value WDI
			- Université de Sherbrooke: extending HR-DTI method for q-ball and high b-value WDI
		MDMRI	- Automatation, Chinese Academy of Sciences: tractography, diffusion MRI data processing
			- Université de Sherbrooke, SCIL: image processing, tractography, data analyses (2016)
3	Oncology	ONCOFLUX	- Max-Planck Institute, Göttingen, Germany: micro-antenna conception
			- University of Pisa, Italy: anti-tumor molecules
4	Neurology	FITTING	- Complex Carbohydrate Research Center, University of Georgia, USA: chemical devolpment
	Oncology	INNOVATHER	- Leipzig University, Germany: synthesis (DOTA-NLS Y1 analogue)
		PRITOR	- INMAS, NewDehli, India: preclinical micro TEP imaging
5	Cardiology	MIMATHUMAB	- Australian 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
	Neurology	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
			- Buffalo University, NY
			- Harvard Medical School: post processing
			- Magnims Network, Buffalo University NY, Royal Holloway London, MS Center Amsterdam
			- MS Center Amsterdam
			- Royal Holloway London
			- Stanford: use of sequence development by Stanford for human application (2015)
		INNES	- UNIL-IP Lausane: providing anti-MCT2 antibodies
		IPALICA	- National Cerebral and Cardiovascular Center, Kyoto-Osaka, Japan (Tomohiro Aoki): physiopathology of aneurism
		SCICOG&REACTIV	- Magnims Network, Buffalo University NY, Royal Holloway London
		TBI	- Loma Linda University, California: vascular biology component
	Oncology	BIOPSYPROS-TAPROBE	- University of Verona (Fracasso & Colombatti): antibodies engineering (2015)
6	Oncology	MOD	- Humanitas Hospital, Milan: glioma
			- University of Alabama at Birmingham (Hassan Fathallah): glioblastoma models
			- Université de Sherbrooke: PET phamacokinetic modeling
	Pneumology	NEKOMRI	- NIH: image reconstruction
7	Neurology	ABACI	- Washington University USA (HCP): population neuroimaging studies (multiple reference spaces)
		ACTE	- SRI International: acquisition, data analysis

WP	APPLIED MEDICAL AREA	TRAIL PROJECT	INTERNATIONAL COLLABORATION
7	Neurology	TRAIL&TRACKS	- Dpt of Neurosciences of Santa Chiara Hospital, Trento, Italy: white matter tracts analysis
			- Sherbrooke University (SCIL): tractography
			- University of Ferrara, Italy: white matter tracts analysis (2013)

D.2 Recruitments (funded by TRAIL)

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

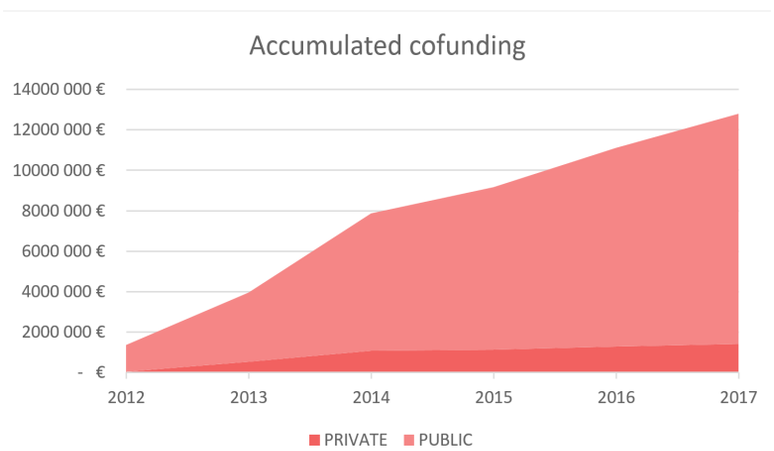
Attractiveness

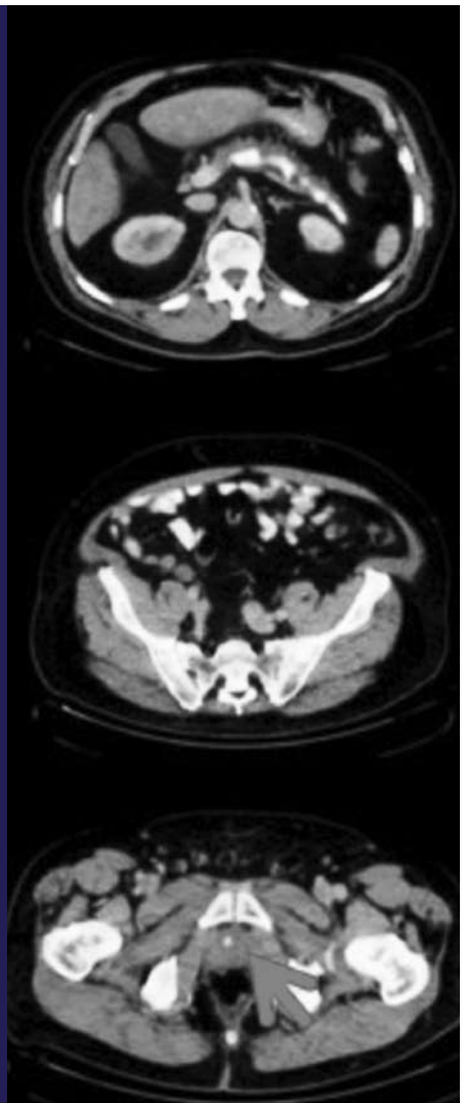
POSITION	WP	TRAIL PROJECT	RECRUITMENTS
Engineer	3	ONCOFLUX	ZHENDRE Vanessa
	4	IMMELAPT	PAURELLE Olivier
		PIAF	MOUGEL Aurélie
	5	TBI	AUSSUDRE Justine
	6	ARM	LAFITTE Luc
		MOD	PIANET Vivien
	7	ABACI	DURIEZ Quentin
			HERVE Pierre-Yves
			LEROUX Gaelle
		ADPP	THEAUD Guillaume
Technician	4	IMMELAPT	BONAZZA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

D.3 Cofunding

COFUNDING PER YEAR	2012	2013	2014	2015	2016	2017	TOTAL
PRIVATE COFUNDING	40 000 €	511 459 €	520 000 €	62 100 €	145 000 €	138 000 €	1 416 559 €
PUBLIC COFUNDING	1 323 800 €	2 090 000 €	3 376 000 €	1 258 007 €	1 785 651 €	1 540 553 €	11 374 001 €
TOTAL	1 363 800 €	2 601 459 €	3 896 000 €	1 320 107 €	1 930 651 €	1678 553 €	12 790 570 €

ACCUMULATED COFUNDING	2012	2013	2014	2015	2016	2017
PRIVATE COFUNDING	40 000 €	551 459 €	1 071 459 €	1 133 559 €	1 278 559 €	1 416 559 €
PUBLIC COFUNDING	1 323 800 €	3 413 800 €	6 789 800 €	8 047 807 €	9 833 458 €	11 374 011 €
TOTAL	1 363 800 €	3 965 259 €	7 861 259 €	9 181 366 €	11 112 017 €	12 790 570 €





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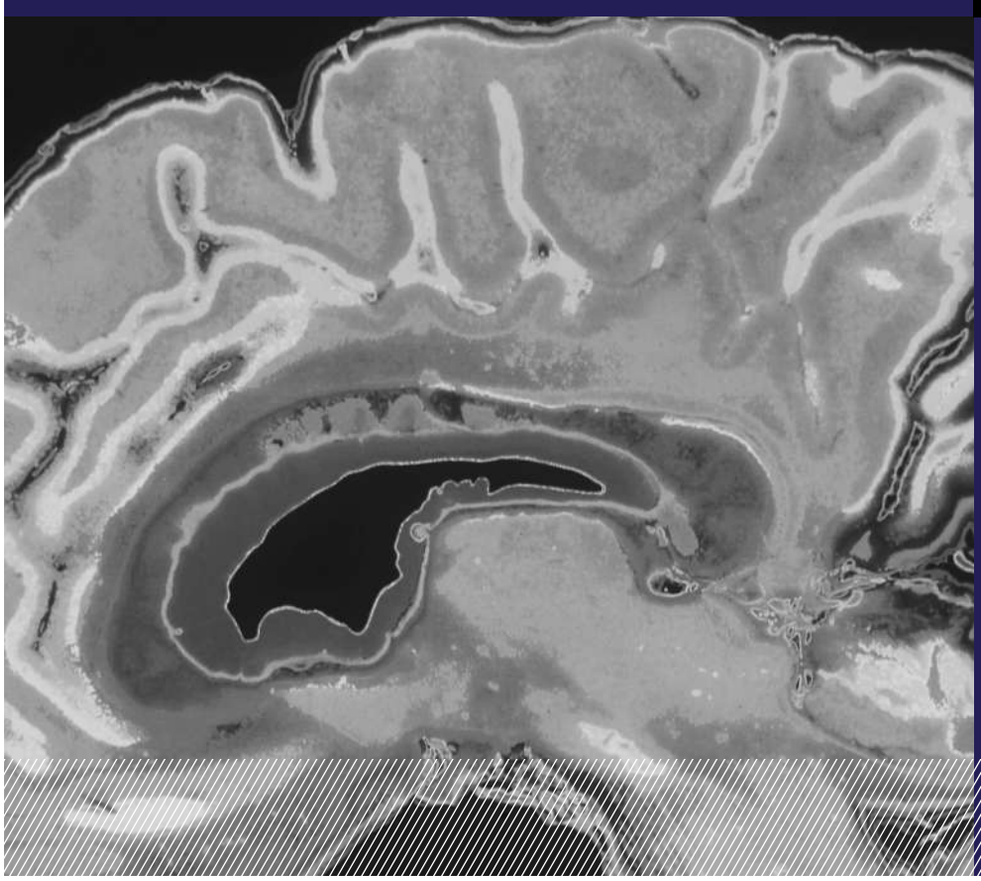

Model and layout : Patrick Cartron, printed by printing office of the University of Bordeaux - February 2018

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Hélène Katz: helene.katz@u-bordeaux.fr

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