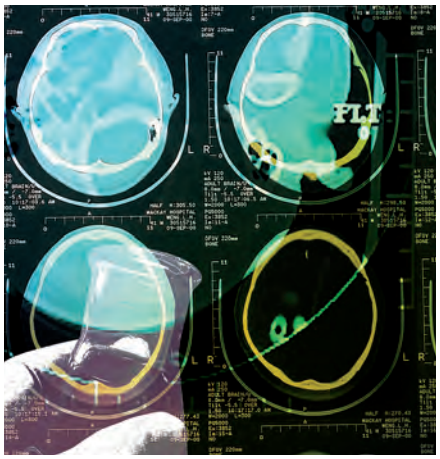
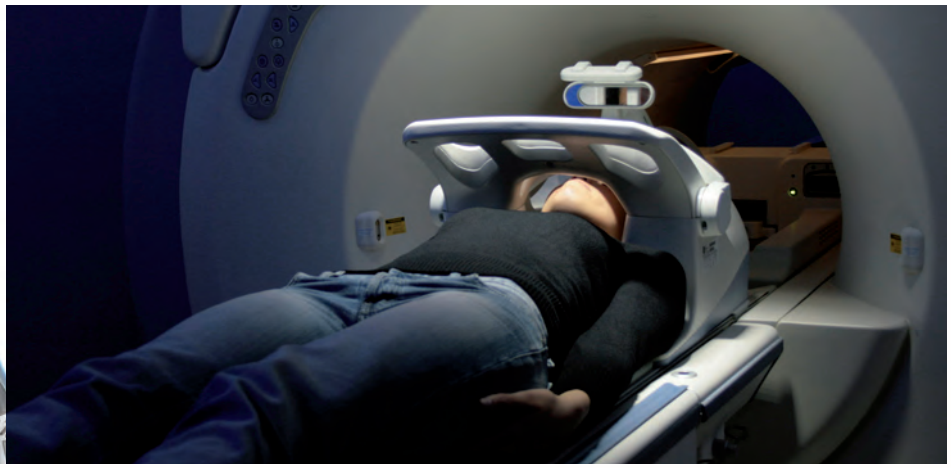
TRAIL

labEx
- initiatives d'excellence -





Translational Research and Advanced Imaging Laboratory

UNIVERSITÉ DE BORDEAUX

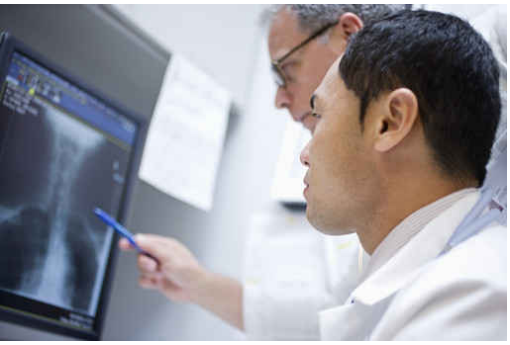
SUMMARY

Effective transfer of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for the prevention, diagnosis, and treatment of disease is essential for improving health. This first step of translational research (T1) refers to the bench to bedside enterprise up to the first testing in humans. It should ideally be followed by the transfer of results from clinical studies into everyday clinical practice and health decision making (T2).

However the process is rarely that simple. The bench to bedside enterprise occasionally yields breakthroughs that markedly improve diagnosis, prognosis, or patient therapies and interventions. Furthermore, the medical environment is rapidly changing: the costs of patient treatments and care are increasing, the budget crisis has encouraged politicians to decrease health spending, diseases are becoming increasingly chronic with patients being treated over a much longer period of time (cancer, cardiac and neurological diseases, …), the population is aging and "personalized medicine" for individual patients is strongly encouraged.
To overcome these difficulties, the European Commission, the French National Research Institutes and the NIH in the US have made translational research a priority, encouraging and forming centers for translational research (60 in the USA by 2012) that take into account all the problems and pitfalls involved in turning new knowledge into clinical practice.

Non - or minimally-invasive imaging technologies are providing researchers with exciting new opportunities to study animal models and human diseases. With continued improvements in instrumentation, identification of better imaging targets and better designed imaging probes using innovative chemistry, imaging technologies promise to play increasingly important roles in disease diagnosis and therapy. Nevertheless, improving patient care while controlling expenditures remains a major goal. Although, imaging techniques are technologically expensive, they may become one of the methods of choice and the "charter" could be described as follows :

- Improving diagnosis through *in vivo* characterization of the cellular and molecular mechanisms of disease in individual patients
- Monitoring treatments or target delivery of therapeutic agents and performing longitudinal evaluation of targeted therapies
- Substituting interventional imaging procedures for surgery
- Serving as surrogate markers of drug efficacy for clinical trials
- Personalizing patient care
- Exploring populations to better understand diseases
- Attracting medical industries to create wealth and employment



The Translational Research and Advanced Imaging Laboratory (TRAIL) program seeks to facilitate interdisciplinary, collaborative basic and clinical research (T1) in image-based diagnostics and novel bio-compatible technologies for evaluating treatments, interventions and drug delivery strategies (see section 5.2). It will also provide evaluation on imaging techniques for patient care, public health impact and medico-economics impact (T2) (see section 5.2.1.3).

In 2007, in Bordeaux, we inaugurated a Bio-Imaging Institute called IBIO that brings together multi-disciplinary human resources (189 people working in the Bio-Imaging field) and task forces (CNRS – CEA - INSERM – University of Bordeaux – University Hospital – Cancer Hospital) around the development of in vivo imaging methodologies and applied sciences for clinical imaging applications. The IBIO is strongly supported by a national and local government grant program CPER of 12Meuros for imaging equipment (4M) and a new facility building (8M) opening early 2013. It is also a priority research program for the University of Bordeaux and several of national research institutes CNRS, INSERM and CEA. Over the past 5 years the research projects of IBIO-partners laboratories have collected 27.5Meuros and more than 60 grants.

The "laboratory of excellence" tender, as part of the "future investments" project, represents an opportunity for IBIO to move forward and create a strong organization for translational research in in vivo imaging called the TRAIL project. With the ultimate objective of significantly contributing to patient care through imaging methods, we seek to create a showcase of talent, training, resources, and facilities that will attract both traditional academic support as well as corporate investment. This goal fully concords with the academic mission of the University to develop and deploy new knowledge and technology related to the improvement of human health, and principally for cancer, neurology, cardiac, lung and kidney diseases.

Our 6 Top goals over the next 10 years are :

- To enhance our fundamental imaging science,
- To reduce obstacles to translational research from bench to bedside,
- To study the impact of our research, new methods and new ima^2-ging technologies on clinical trials, personalized medicine, patient care, epidemiology and socio-economic impact,
- To provide a single open portal and showcase promoting relationships with industrial partners in the vicinity of Bordeaux as well as on a national and international level,
- To promote education for appropriate job qualifications and better social integration,
- To set up a strong governing organization and an internal management

The composition of TRAIL – CORE partners

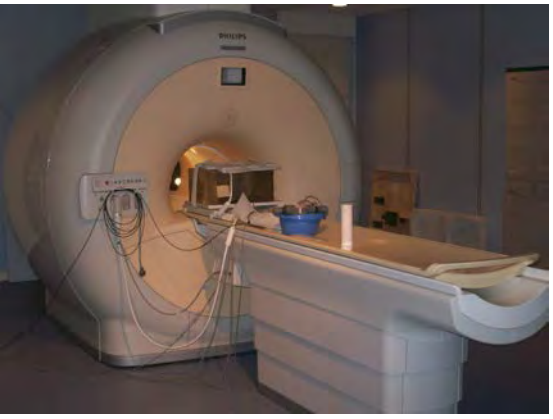
The core **partners** are eight teams from seven research laboratories, all being units from the national research institutes CNRS, CEA, INSERM, and setting at Universities of Bordeaux 2 and Bordeaux 1, made up of researchers, engineers and teachers/researchers (n=189).

- **Magnetic Resonance of Biological Systems Laboratory** (CNRS/UB2 Unit) – Unit Head: JM Franconi, PhD
- **Bio-active molecules and Synthesis Team** – Head: E Fouquet, PhD - Molecular Sciences Institute (CNRS/UB1 Unit) – Unit Head: P Guarrigues, PhD
- **Cardiac ElectroPhysiology Team** – Head: M Haissaguerre, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD
- **Bronchial Remodeling Team** – Head: P Berger, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD
- **Neurofunctional Imaging Group** (CNRS/CEA/UB2 Unit) – Unit Head: B. Mazoyer, MD, PhD
- **Neurofunctional and Cognitive Imaging Team** – Head: M Allard, MD, PhD - INCIA (CNRS/UB1/UB2 Unit) - Unit Head: JR Cazalets, PhD
- **Neurobiology of Myelin Diseases Laboratory** (INSERM U 1049/UB2 Unit) – Unit Head: KG Petry, PhD
- **Centre of Clinical Investigation in clinical Epidemiology CIC-EC7 INSERM – Bordeaux 2 University – Bordeaux University Hospital / Bergonié Cancer Institute** (INSERM 2010 A) G. CHENE MD PhD and P. PEREZ MD PhD

UB2: University Bordeaux 2; UB1: University Bordeaux 1; CNRS: Centre National de la Recherche Scientifique; INSERM : Institut National de la Santé et de la Recherche Médicale ; CEA : Commissariat à l'Energie Atomique

A federation of laboratories and teams working on imaging research constitutes the core of LabEx working towards translational research in imaging. Physicists, chemists, biologists and physiologists from CNRS, INSERM, CEA, University faculties and medical staffs meet the criteria of excellence to join TRAIL. They have substantial experience in sharing research and will work together on the T1 bench to bedside steps described below.

The partners are helped by **ten collaborators,** defined as major research teams in the same area as the partners and with whom collaboration is essential to develop translational imaging research. Several of those collaborative teams are involved in other Laboratory of Excellence projects creating a pull effect in the close environment of TRAIL. One partner is identified as developing socio-economic studies and evaluating the patient-care impact of our research (T2 steps).



Our project is helped by well-identified **nine support service structures** that allow and foster basic research, clinical research or technology transfer. They include the Bordeaux University Hospital clinical research support services and the cancer hospital of Bordeaux, two of the leading hospitals in France. Technology transfer will be promoted through a newly elaborated structure that merges hospital clinical research with pharmaceutical and technological industries: "Bordeaux Recherche Clinique".

We defined 7 Work-Packages (WP) according to either recognized excellence (5/7) or emerging original risk-taking topics (R* 2/7):

↘WP1: **MR Guided High Intensity Focused Ultra Sounds** – B Quesson CNRS / UB2

↘WP2: **New MRI Contrasts – New MRI Sequences** – JM Franconi UB2/CNRS - S Miraux CNRS/UB2

↘WP3R*: **Dynamic Nuclear Polarization** – JM Franconi UB2/CNRS - E Thiaudière UB2/CNRS

↘WP4: **Radiopharmaceutical Tracers and Contrasts Agents** – E Fouquet CNRS / UB1 - M Allard UB2 /CNRS/CHU

↘WP5: **Targeted Biological Markers for Bio-Imaging** – KG Petry INSERM/UB2

↘WP6R*: **Mathematical Simulation and Modelling** – J Palussiere CLCC/CNRS - P Jaïs UB2/INSERM/CHU

↘WP7: **Structural/functional neuroimaging tools for preclinical, clinical and population studies** – B. Mazoyer CNRS/CEA/UB2

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Interactive Researches for Translational Research between WP and Applied Medical Fields

	WP1 MRI guided HIFU	WP2 New Contrast / New Sequences	WP3 DNP	WP4 Tracers and Contrast Agents	WP5 Biological Bio-Imaging Markers	WP6 Mathematic Simulation and Modelling	WP 7 Methodology Neuro-Imaging	WP8 Translational methodology
Oncology J Palussière Ph Fernandez C Moonen F Couillaud H Trillaud	Interventional MRI and		Tumor Metabolism	Tumor Metabolism	Tumor Molecular Imaging	Tumor growth modelling		
Neurology B Mazoyer M Allard V Dousset B Hiba		Aging brain		Functional PET Imaging Aging brain	Inflammation Imaging		Functional MRI Cohorts Human MRI 7T	
Cardiology M Haissaguerre P Jaïs B Quesson H Cochet	Interventional MRI for cardiac ablation	3D coronary velocity mapping		Cardiac Purkinje Network Targeting		Modeling of cardiac electrical disorders		
Pneumology P Berger F Laurent Y Crémilleux		Bronchial wall Imaging	Metabolic and molecular imaging		Inflammation imaging			
Nephrology N Grenier B Denis de Senneville Ph Fernandez		Kidneys Functional MRI			Inflammation Imaging and fibrosis			

The development of each WP fosters the development of translational research with imaging specialties. Our choice takes into account the existing excellence of research in those particular fields as attested by rate of publications, patents, evaluations from national research agencies, international attractiveness, etc. Themes: Oncology, Neurology, Cardiology, Pneumology, Nephrology.

The Trail project is supported by an imaging platform that offers the multiple accesses for pre-clinical and clinical research works:

↘**MRI and Spectroscopy for small animal:** 0.2T MR imaging system; 4.7T MR imaging system; 7T MR imaging system (2010); 9.4 T spectrometer and imaging system 400MHz; 11T spectrometer 500MHz

↘**MRI for Human and for large animals Pre-clinical Molecular and Functional Imaging:** 1.5T MRI system; 3T MRI system

↘**MRI for Human at hospitals facilities for clinical research:** 4 x 1.5T Clinical Systems (one with HIFU) University Hospital Bordeaux; 3T MR imaging system (2010) University Hospital Bordeaux; 1.5T Clinical System with HIFU Cancer Institute Bordeaux

↘**PET for Human clinical research and for large animals pre-clinical:** PET/CT Research Imaging System University Hospital Bordeaux

↘**Optical Imaging:** *2 In vivo* Optical Imaging Systems

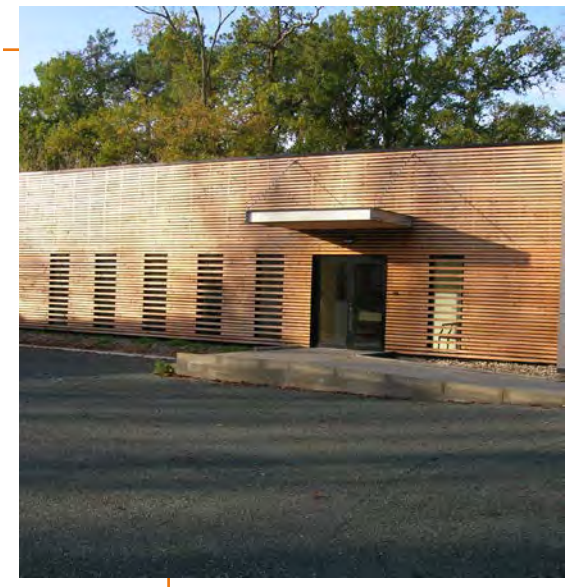
In order to be consistent with our laboratory of excellence TRAIL aims and to foster our research, we have responded to several of the calls from "investissement d'avenir" to acquire 4 types of cutting-edge equipment:

- EquipEx: Micro-Cyclotron + MicroPET/SPECT/CT (PRECLIMI) for WP4 and WP5
- EquipEx: 3.0T Interventional MRI in cardiac imaging (EP-XMR) for WP1 and WP6
- InfraStructure Nationale*: 7.0T MRI for Human clinical research for WP7
- InfraStructure Nationale*: 7.0T MRI for pre-clinical application and translational research for WP2, WP4, WP5 and WP7

** a national platform of 3 x 7.0 T MRI for human clinical research with Universities of Marseille, Lyon and Grenoble.*

CONCLUSION

Based on our extensive background in imaging research, and support from national institutes for research, from local and government research departments, and from one of the top three university hospitals in France, we aim to become one of the leading sites in Europe with international recognition for our topics of interest in translational research and imaging.



Letters of support and Intend situated in Annexe 7.5 are from: the President of the University of Bordeaux, the President General Director of INSERM National Institute, the Scientific Director of CNRS National Institute, and from several private corporates: the General Manager of AGFA Healthcare, the President of General Electric Healthcare France, the Director Imaging and Therapy of Siemens, the Clinical Science Director of Philips, the Research and Development Director of Guerbet, the director of Sanofi-Aventis, the director of CRO ITEC.

01/

Application to the actions of the programme “investissements d’avenir”

The following figure summarizes several applications to the Actions of the national programme Investissements d'Avenir, and their link with TRAIL.

Top line - **Initiative of Excellence**

the University of Bordeaux, chosen in 2008 by Operation Campus among the 10 top sites in France, has decided to seize the opportunity of the national Inititiative d'Excellence call to accelerate its development.

Second line - **Laboratory of Excellence**

The University of Bordeaux conceives a laboratory of excellence (LABEX) as a grouping of research teams whose excellence is widely recognized (within the terms of the discipline concerned), who have wide international visibility and who are willing to contribute to an ambitious innovative research project. Of key importance is the project's capacity to promote the valorization of research, whether in terms France's research reputation or in terms of direct socio-economic benefits (development, training). The University of Bordeaux is promoting eight "Laboratory of Excellence" projects among which several are associated by design with our proposal of TRAIL Labex: "SP2 (METIS)" on health and society issues, "BRAIN" on basic neurosciences, "TIC (CPU)" on numerical certification and "AMADEUS" on advanced materials. Teams within these different LabEx projects are currently collaborating with several teams of TRAIL and intend to promote stronger collaborations through the pull effect given by the LabEx call.

Institut Hospitalo-Univesitaire: We are linked to the LIRYC project, a call for IHU "Institut Hospitalo-universitaire", based on Bordeaux's excellence in cardiology and rythmology. One of our applied medical imaging fields is in cardiology (see section 5.2 scientific program).

Third line – **Equipment of Excellence:**

In September 2010 we have applied for two EquipEx calls (results not yet announced) that are necessary to develop our research:

- PreClimi: a Micro-cyclotron and a MicroPET/SPECT/CT that will foster our research on bio-imaging markers (WorkPackage 5) and on Tracers (WorkPackage 5). It will allow translational research with pre-clinical imaging in the aim of reaching the clinical level through our full-time research-orientated PET/CT for humans. A commitment from the General Electric company has been obtained for this project.
- EP-XMR: a 3.0 Tesla MRI coupled with an X-Ray angio room for developing innovations in the field of interventional MRI in cardiac imaging. This will foster the development of HIFU applied to the heart (WorkPackage 1) and cardiac modeling and simulation (Work Package 6).

In addition we aim at developing innovative risk-taking research (Work Package 3) concerning Dynamic Nuclear Polarization, a very challenging new technology in the field of MRI. The investment will require that we apply in 2011 or 2012 for a future grant call for Equipment of Excellence. The commitment of the Siemens company has been obtained for this project.

Fourth line – **National InfraStructure:**

In October 2010 we applied to this grant call (results not yet announced) for a project together with the universities of Marseille, Lyon and Grenoble to promote a national platform and network (NMRINet) of technology and knowledge for human MRI operating at 7.0 Tesla. In this call, our Bordeaux site has asked for one MRI at 7.0 T (for Work Package 7, applied to neurology) and a small animal MRI operating at 7.0 T for making the translation of research from animals to humans easier. The commitment of the General Electric company and Bruker company have been obtained for this project.

The several components of the “Investment of Avenir” initiative will allow us to reach the level of an international expert center in translational bio-imaging research.

02/

Management of the the partnership

Composition of the partnership

The LabEx project is composed of 7 laboratories with complementary expertise on bioimaging research.
Among these laboratories 8 teams will be directly involved in the LabEx:

▶**Magnetic Resonance of Biological Systems Laboratory** (CNRS/UB2 Unit) – Unit Head: JM Franconi, PhD

▶**Bio-active molecules and Synthesis Team** – Head: E Fouquet, PhD - Molecular Sciences Institute (CNRS/UB1 Unit) – Unit Head: P Guarrigues, PhD

▶**Cardiac ElectroPhysiology Team** – Head: M Haissaguerre, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD

▶**Bronchial Remodelling Team** – Head: P Berger, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD

▶**Neurofunctional Imaging Group** (CNRS/CEA/UB2 Unit) – Unit Head: B. Mazoyer, MD, PhD

▶**Neurofunctional and Cognitive Imaging Team** – Head: M Allard, MD, PhD - INCIA (CNRS/UB1/UB2 Unit) - Unit Head: JR Cazalets, PhD

▶**Neurobiology of Myelin Diseases Laboratory** (INSERM U 1049/UB2 Unit) – Unit Head: KG Petry, PhD

▶**Centre of Clinical Investigation in clinical Epidemiology CIC-EC7 INSERM – Bordeaux 2 University – Bordeaux University Hospital / Bergonié Cancer Institute** (INSERM 2010 A) G. CHENE MD PhD and P. PEREZ MD PhD

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Demography

Lab Name	*Affiliation*	*Staff*	
Magnetic Resonance of Biological Systems Laboratory (UMR 5536)	UB2 - CNRS	8 Researchers	12 Teacher-researchers
		4 Post doc	4 PhD students
		8 IATOS-Engineers	14 Other IATOS
Molecular Sciences Institute (UMR 5255)	UB1-IPB-CNRS	3 Researchers	7 Teacher-Researchers
		6 Post doc	16 PhD students
		2 IATOS-Engineers	4 Other IATOS
Cardio-Thoracic Research Center of Bordeaux - Cardiac ElectroPhysiology Team	UB2 - INSERM	0 Researcher	6 Teacher-researchers
		3 Post doc	2 PhD students
		0 IATOS-Engineers	0 Other IATOS
Cardio-Thoracic Research Center of Bordeaux - Bronchus Remodelling Team	UB2 - INSERM	1 Researchers	9 Teacher-researchers
		1 Post doc	5 PhD students
		2 IATOS-Engineers	1 Other IATOS
Neurofunctional Imaging Group (UMR 6232)	UB2 - CNRS - CEA	5 Researchers	3 Teacher-researchers
		1 Post doc	4 PhD students
		2 IATOS-Engineers	1 Other IATOS
INCIA	UB1 - UB2 - CNRS	2 Researchers	6 Professors-Assistant Professors
		2 Post doc	5 PhD students
		2 IATOS-Engineers	2 Other IATOS
Neurobiology of Myelin Diseases Laboratory (INSERM U 1049)	UB2 - INSERM	2 Researchers	4 Teacher-researchers
		3 Post doc	4 PhD students
		1 IATOS-Engineers	1 Other IATOS
Total		**25 Researchers**	**52 Teacher researchers and Professors**
		21 Post doc	**47 PhD students**
		19 IATOS-Engineers	**25 Other IATOS**
Total	**LabEx TRAIL**	**189 workers on the topic of TRAIL**	

The LabEx TRAIL: overview of Skills and Know-How of Partners (core), Collaborators and Supportive Structures

↘ Partners

The **partners** are defined as laboratories or teams fully dedicated to imaging research, the federation of which constitutes the core of the LabEx focus on translational research in imaging.

➨ **Magnetic Resonance of Biological Systems Laboratory** (CNRS/UB2 Unit) – (AERES 2010 A) - Unit Head: JM Franconi, PhD
Physicists and biologists specialized on MRI methodology with pre-clinical assessment
Research on new MR contrasts and new MR sequences – Risk-taking research on Dynamic Nuclear Polarization
Involved in WP 2 and WP 3 – Applied to Oncology – Neurology - Cardiology – Pneumology

➨ **Bio-active molecules and Synthesis Team** – (AERES 2010 A+) - Head: E Fouquet, PhD - Molecular Sciences Institute (CNRS/UB1 Unit) – Unit Head: P Guarrigues, PhD
Chemists specialized in the development of new methodologies in organic and organometallic chemistry for two purposes: 1) Reactions taking care of environmental concerns, and application to the synthesis of bioactive molecules. 2) Fast and practical methodology to be applied to the radiolabelling of ligands for TEP Imaging.
Involved in WP 4 – Applied to Oncology and Neurology

➨ **Cardiac ElectroPhysiology Team** – (AERES 2010 A+) - Head: M Haissaguerre, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD
A world class team with high recognition on cardiac rythmology.
Interventional MRI and Heart Modeling
Involved in WP 1 and WP 6 – Applied to Cardiology

➨ **Bronchial Remodeling Team** – (AERES 2010 A+) - Head: P Berger, MD, PhD - Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) – Unit Head: R Marthan, MD,PhD
An international leader team on the role of bronchial smooth muscle in asthma and chronic obstructive pulmonary disease pathophysiology. An attractive team focused in translational respiratory medicine involving physiologists, biologists, chest physicians, pharmacologists, physicists and radiologists.
Involved in WP 2, WP 3, WP 4 and WP 5 – Applied to Pneumology

➨ **Neurofunctional Imaging Group** (GIN, CNRS/CEA/UB2 Unit) – (AERES 2010 A) -Unit Head: B. Mazoyer, MD, PhD
This unit has pioneered brain activation studies in France and contributed to the emergence of the cognitive neuroimaging domain at the International level. Its staff has extensive expertise in the set-up and operation of brain imaging facilities, and has made several key contributions both in image analysis and in the cognitive neuroscience of language and visio-spatial functions. The GIN has also pioneered population brain imaging for research on aging, and is currently acquiring and analyzing a large MRI database for the study of human brain variability. GIN researchers have trained more over 30 PhD's and organized three summer schools.

Involved in WP 2 & WP 7 – Applied to Neurology

- **Neurofunctional and Cognitive Imaging Team** – (AERES 2010 A) - Head: M Allard, MD, PhD - INCIA (CNRS/UB1/UB2 Unit) - Unit Head: JR Cazalets, PhD

A multi-disciplinary team examining disorders such as stroke, dementia and age-related cognitive decline using a unique combination of research paradigms.

Involved in WP2, WP4, WP 5 and WP 7 Applied to Neurology

- **Neurobiology of Myelin Diseases Laboratory** (INSERM/UB2 Unit) – (AERES 2010 A) - Unit Head: KG Petry, PhD

A European competitive translational research team on Brain Inflammation and Multiple Sclerosis – Skills in Biology, imaging and clinical research

Involved in WP2, WP4, WP 5 and WP 7 Applied to Neurology

- **Centre of Clinical Investigation in clinical Epidemiology CIC-EC7 INSERM – Bordeaux 2 University – Bordeaux University Hospital / Bergonié Cancer Institute** (INSERM 2010 A) G. CHENE MD PhD and P. PEREZ MD PhD

Clinical research, large cohorts, methodological innovations (epidemiology, biostatistics)

Involved in T2 Translational Research

Collaborators

To achieve our research goals, we are working with **collaborators** defined as the major research teams of the TRAIL partners and with whom collaboration is essential to develop translational imaging research.

- **Labo ARNA (*ARN: Régulations Naturelles et Artificielles*) (A+); team "Small RNAs and Aptamers"** (AERES 2010 A) JJ TOULME, PhD
Research on Aptamers
Collaborate for biological targets (WP5) and new contrasts agents (WP4)

- **Institut de Mathématiques de Bordeaux and INRIA MC2** (AERES 2010 A+) T COLIN PhD
The team develops numerical models for tumor growth that are patient specific based on medical imaging.
Collaborate for mathematical simulation and modeling (WP6) and for oncology (AE1).
Pull effect on LabEx TIC: Numerical certification, reliability and proof of systems

- **LaBRI Laboratoire Bordelais Recherche Image** (AERES 2010 A+) P WEIL PhD
Contribution in the field of image processing and analysis (e.g. MRI, PET, CT imaging).
Pull effect on LabEx TIC

- **ICMCB-CNRS UPR 9048 Group 5 "Chemistry of Nanomaterials"** (AERES 2010 A+) E Duguet PhD
Tailor-made MRI contrast agents and dye-labeling based on inorganic nanoparticles
Collaborate to WP4 tracers and contrast agent and to WP5 biomarkers for bio-imaging
Pull effect on LabEx Advanced Materials by Design

- **IMN: Institute of Neuro-degenerative diseases (CNRS Unit)** Team (AERES 2010 A+) E Bezard PhD
Translational development of therapeutic strategies for parkinsonian syndromes from animal models to patients. WP7 applied Neurology
Pull effect LabEx Neurosciences

- **IMN: Institute of Neuro-degenerative diseases** (CNRS Unit) Team (AERES 2010 A+) Bruno BONTEMPI PhD
Physiology and pathophysiology of cortico-subcortical relationships in support of memory formation and retrieval, integrating the key role of vascular function and modulation. WP7 applied Neurology
Pull effect LabEx Neurosciences

- **Epidemiology and Bio-Statistics INSERM/ISPED/UB2 Team Epidemiology and Neuropsychology of Brain Aging** (AERES 2010: A) JF DARTIGUE MD,PhD
Cohorts: Paquid – 3 Cités – MSA – ALZ – Bordeaux Etudiants
Population-based cohort studies on normal and pathological brain aging. Repeated MRI at successive follow-up screening on unselected participants. WP7 applied Neurology
Pull effect LabEx SP2: Health, Society, Politics

- **Laboratoire Biomatériaux et Ingénierie Tissulaire Inserm U577** (AERES 2010: A) J. AMEDEE VILAMITJANA PhD
Collaboration for therapeutic strategies for tissue regeneration and imaging of implanted mesenchymal stem cells. WP5 Bio-imaging markers applied to Nephrology
Pull effect on LabEx Advanced Materials by Design

- **Chemistry and Biology of Membrane and Nano-Objects – CNRS UMR 5248** – (Aeres A+) EJ DUFOURC PhD
Research on spectroscopic and optical techniques for nanoimaging
Collaborate for new contrast agents (WP4) and biological targets (WP5)

Support Structures

To develop our research, the TRAIL will be supported by several support structures defined as organizations that allow and foster basic research, clinical research or valorization.

- **CHU de Bordeaux** A Hériaud General Director

The 3300 bed University Hospital of Bordeaux has one Radiology and Nuclear Medicine department of 500 employees with dedicated technicians, 4 clinical research assistants and one supervisor for clinical research imaging

- **Direction Recherche Clinique et Innovation CHU de Bordeaux** JP Leroy Directeur, J Boussuge – N Hayes collaborators

The clinical research and innovation Direction of the Bordeaux Hospital is composed of 4 departments: academic sponsorship department, industrial sponsorship department, biotechnological innovation department and a financial department

- **Center of Clinical Investigation Pluri-thematic CIC-P CHU de Bordeaux** N Moore Director, S Blazejewski collaborator

The Bordeaux Clinical Investigation Centre (CIC) is a federation of clinical research teams driving translational projects in collaboration with labeled experimental labs.

The CIC performs clinical research in the special interest areas of Neurosciences, Oncology, Chest Diseases, Cardiology and Pharmacoepidemiology.

- **Clinical research Unit (USMR) University Hospital Bordeaux** G. Chêne MD, PhD, Director, P Perez collaborator MD, PhD

Clinical research, epidemiology, biostatistics, informatics, data management

- **Centre de Lutte Contre le Cancer** J Reiffers General Director

A dedicated hospital for treatment, education and research against cancer

Participation of the Radiology and Nuclear Medicine Department for Clinical Research

- **GBRC : Bordeaux Clinical Research Network**

A one-stop-solution for industry sponsored clinical trials (pharmaceutical, medical devices and nutritional industries)

- **Aquitaine Valo (SATT) University of Bordeaux** . Directror Maylis Chusseau - Technology Transfer office or the University of Bordeaux

- **2ADI: Aquitaine Agency for Industrial Development** J PASSEMARD Director, V LASCAUX collaborator engineer

2ADI supports the organization of the TRAIL LabEx as part of the forthcoming Healthcare Cluster, promotes links with industrial companies and attraction of new investors.

- **Foundation Bordeaux Universities** JR FOURTOU President R GOUIN Director

Nonprofit organization, raising funds to support the best research and education projects.

RELEVANT EXPERIENCE OF THE PROJECT COORDINATOR

Vincent Dousset, MD, PhD

Professor of Radiology and Medical Imaging
Teacher/Researcher in the Neurobiology of Myelin Diseases Laboratory (INSERM Unit)
Vice-President of the University Victor Segalen Bordeaux 2 for External Relations
Department Chairman of Radiology and Nuclear Medicine University Hospital of Bordeaux

Curriculum : Born in 1961, qualified as an MD specialist in Radiology and Medical Imaging in 1991. I trained as a Research Fellow at the University of Pennsylvania in the Department of Radiology and Nuclear Medicine in 1990 and 1991. During that period, I was introduced to pre-clinical research on a model of inflammatory disease of the CNS, then moved on to clinical application on Multiple Sclerosis patients. I was awarded a Masters degree in Health and Biology in 1994 and obtained my PhD degree in Health and Biology in 1997 from the University of Bordeaux 2.

Research skills : My research focuses on translational research from bench to bedside with the overall goal of serving patient diagnosis or therapy.

Researcher Profile: Peer review papers (source PubMed) = 116; Sum of times cited: 4399; Average Annual citation index = 218; Average citations per paper = 30; H Index = 31 (sources ISI Web of Knowledge Oct. 2010) .

Three examples :

- **Magnetization Transfer Imaging applied to the CNS**

This work was initiated during the time spent as a guest researcher at the Department of Radiology at the University of Pennsylvania in 1990-1991. We found and established the MTR ratio: a robust and reproducible value to quantify *in vivo* tissue destruction by MRI (Dousset et al; Radiology 1992 Citations n=482). The work was started on animals with experimental acute encephalomyelitis with histological correlations. We moved on to multiple sclerosis patients and showed how to quantify tissue breakdowns including tissue that appeared normal with conventional MR. MTR is now available as a standard application on all routine MR scanners and MTR is used in clinical trials in the CNS (Tourdias et al; Stroke 2007 IF=6.3) and other organs as a surrogate marker of the efficacy of a therapy. This work has received several awards (European Association of Radiology; 1st Lucien Appel Price European Society of Neuroradiology; …)

- **MR Diffusion Imaging of the Spinal Cord**

We developed a new sequence for the challenging exploration of the spinal cord with diffusion imaging (Ries et al; Magn Reson Med, 2000 citations n=70). The initial work received an award from the American Society of Neuroradiology in 1997 (best paper award). We applied the sequence to patients with spinal cord compression and showed its usefulness over conventional sequences (Demir et al; Radiology 2003 citations n=36)

- **Ultra-Small Particle Iron oxide (USPIO) applied to macrophage imaging in the CNS**

  We demonstrated, for the first time, that this new contrast agent might be used to target the presence of macrophages in the brain during inflammatory processes (Dousset et al; Magn Reson Med 1999 citations n=113; Am J Neuroradiol 1999 citations n=74). The work has now been applied to patients with multiple sclerosis (Dousset et al; Am J Neuroradiol 2006 citations n=59). I have written a collaborative review paper on this topic (Bakshi et al; Lancet Neurol 2008 IF=14.2). We recently obtained a national research grant (translational research grant INSERM-Ministery of Health) of 100.000 Euros to use USPIO at 7.0 Tesla in patients with MS.

I am now dedicating most of my research time, in collaboration with a PhD student, a Japanese post-doc and a technician, to studying the regulation of oedema of experimental CNS inflammatory processes and its *in vivo* approach on animals and humans, with MRI and diffusion imaging (Tourdias et al; NeuroImage 2009 IF=5.7).

Management skills:

In 2001 I became head of the Neuroradiology Unit at the University Hospital of Bordeaux (CHU).
From 2005 to 2007, I was asked to work on setting up a single Radiology and Nuclear Medicine Department. **From 2007 until now I am the Chairman of this Department which has 500 employees, with 65 physicians, and eight clinical imaging units spread across three hospitals.** The department receives more than 375000 patients a year, and all units are involved in the training and teaching of all categories of students. It is one of the top research departments in the University Hospital (rank3/24) with around 75 ongoing clinical research trials (Oct. 2010).
I also assist the director of the research laboratory (Laboratory of the Neurobiology of Myelin Diseases) in determining scientific strategy and the management of laboratory colleagues and employees. The Lab has been significantly promoted this year to become an INSERM (French National Institute of Health) laboratory starting on January 1st, 2011.
In 2009, the Dean of the University of Bordeaux 2 called on me to coordinate the creation of the Bordeaux Institute of Bio-Imaging which has several trustees: University Bordeaux 2, National Research Institutes (CNRS, INSERM), University Hospital and Cancer Hospital. This federation of eight imaging research laboratories aims at promoting translational research. These labs constitute the core of the TRAIL project we are presenting here.

Teaching Skills:

I teach several hours per week at the Medical School of the University Victor Segalen Bordeaux 2. I am regularly invited as an international lecturer by many scientific societies. I received the Outstanding Teacher Award from the International Society of Magnetic Resonance in Medicine (2008). I am regularly invited as a visiting professor to the University of Kyoto. Most recently, we created a new leading-edge Masters Course entitled the International Master of Bio-Imaging at the University Victor Segalen Bordeaux 2 starting in 2011 in collaboration with Laval University in Canada.

Most representative publications of coordinator for translational research:

	Impact Factor	Citations
Tourdias T, Dragonu I, Fushimi Y, Deloire MS, Boiziau C, Brochet B, Moonen C, Petry KG, Dousset V. **Aquaporin 4 correlates with apparent diffusion coefficient and hydrocephalus severity in the rat brain: A combined MRI-histological study.** Neuroimage. 2009 Aug 15;47(2):659-66. Epub 2009 May 3	**5.739**	**2**
Bakshi R, Thompson AJ, Rocca MA, Pelletier D, Dousset V, Barkhof F, Inglese M, Guttmann CRG, Horsfield MA, Filippi M. **MRI in multiple sclerosis: current status and future prospects.** Lancet Neurol. 2008 Jul;7(7):615-25	**14,270**	**34**
Tourdias T, Dousset V, Sibon I, Pelé E, Ménégon P, Asselineau J, Pachai C, Rouanet F, Robinson Ph, Chêne G, Orgogozo JM. **Magnetization transfer imaging shows tissue abnormalities in the reversible penumbra.** Stroke. 2007 Dec;38(12):3165-71	**6.296**	**3**
Demir A, Riez M, Moonen CTW, Vital JM, Dehais J, Arne P, Caillé JM, Dousset V. **Diffusion-weighted MR imaging with apparent diffusion coefficient and apparent diffusion tensor maps in cervical spondylotic myelopathy.** Radiology. 2003 Oct;229(1):37-43	**4.815**	**36**
Ries M, Jones RA, Dousset V, Moonen CT. **Diffusion tensor MRI of the spinal cord.** Magn Reson Med. 2000 Dec; 44(6):884-92	**3.121**	**70**
Dousset V, Ballarino L, Delalande C, Coussemacq M, Canioni P, Petry KG, Caille JM. **Comparison of ultrasmall particles of iron oxide (USPIO)-enhanced T2-weighted, conventional T2-weighted, and gadolinium-enhanced T1-weighted MR images in rats with experimental autoimmune encephalomyelitis.** AJNR Am J NeuroRadiology. 1999 Feb;20(2):223-227	**2.358**	**74**
Dousset V, Delalande C, Ballarino L, Quesson B, Seilhan D, Coussemacq M, Thiaudière E, Brochet B, Canioni P, Caillé JM. **In vivo macrophage activity imaging in the central nervous system detected by magnetic resonance.** Magn Reson Med. 1999 Feb;41(2):329-33	**3.757**	**113**
Dousset V, Grossman RI, Ramer KN, Schnall MD, Young LH, Gonzalez-Scarano F, Lavi E, Cohen JA. **Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with Magnetization Transfer imaging.** Radiology. 1992 Feb;182(2):483-91	**3.307**	**482**

03/

Description of the existing

Presentation of partners

The **PRES/Université de Bordeaux** as coordinating partner is by definition the **partner 1.**
The University of Bordeaux is today one of the leading campuses in France, comprising more than 5 000 academic staff and around 60 000 students (including 3 000 PhD candidates). For more details, see the description of the University of Bordeaux in the **Annex 7.6.1** and the description of its strategy within the programme *Investissements d'Avenir* in **section 5.3.**

Presentation of LabEx teams -Partners 2 to 8

Partners are defined as fully dedicated laboratories or teams to imaging research, the federation of which constitutes the core of the LabEx to aim at translational research in imaging.
Presentation at a glance :

PARTNERS (CORE)	HEAD TEAM	AERES 2010	Skills and Know-How
Laboratory Magnetic Resonance of Biological Systems (CNRS/UB2 Unit)	JM FRANCONI PhD H Index: 14	A	Physicists and biologists specialized on MRI methodology with pre-clinical assessment. Research on new MR contrasts and new MR sequences
Molecular Sciences Institute (CNRS/UB1 Unit) Bio-active molecules and Synthesis Team	E FOUQUET PhD H Index : 17	A+	Chemists specialized in the development of new methodologies in organic and organometallic chemistry.
Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) Cardiac ElectroPhysiology Team	M HAISSAGUERRE MD H Index : 61	A+	A world class team with high recognition on cardiac rythmology. Interventional MRI and Heart Modelling
Cardio-Thoracic Research Center of Bordeaux (INSERM/UB2 Unit) Bronchus Remodeling Team	P BERGER MD PhD H Index : 17	A+	An attractive team focused in translational respiratory medicine involving physiologists, biologists, chest physicians, pharmacologists, physicists and radiologists.
Neuroscience Imaging Group (CNRS/CEA/UB2 Unit)	B MAZOYER MD PhD H Index : 51	A	This unit has pioneered brain activation studies in France and population brain imaging for research on aging
INCIA (CNRS/UB1/UB2 Unit) NeuroFunctional and Cognitive Imaging Team	M ALLARD MD PhD H Index : 27	A	A multi-disciplinary team examining disorders such as stroke, dementia and age-related cognitive decline using a unique combination of research paradigms.
Neurobiology of Myelin Diseases Laboratory (INSERM/UB2 Unit)	KG PETRY PhD H Index : 27	A	A European competitive translational research team on Brain Inflammation and Multiple Sclerosis – Skills on Biology, imaging and clinical research
CIC EC7	P Perez	A	*methodological innovations*

Research and innovation

↘ Overview of research projects of TRAIL teams

➨ **Partner 1** : University of Bordeaux

➨ **Partner 2 : Magnetic Resonance of Biological Systems Laboratory (UMR CNRS 5536), Unit JM. Franconi**

The UMR5536 expertise is clearly situated in the field of the living organism exploration by NMR imaging and spectrometry. We are able to develop and propose:
- very innovating concepts, methods and instruments (mouse flow quantification method, in vivo nuclear dynamic polarization, new concepts of contrast agent quantification for molecular imaging)
- new strategies of metabolic and functional exploration for the understanding of living systems (role of lactate in the cerebral metabolism, control analyses of the cardiac and skeletal contractile function, understanding of metabolism in parasites)
- innovating methods of in vivo cellular and molecular targeting and marking followed by MRI (follow-up of glial cells like vectors for the cellular and gene therapy against the gliome, visualization of the unstable atheroma plaque).

Radiology. 2010 Feb;254(2):441-8 ; NMR Biomed. 2010 Jan;23(1):88-96 ; Proc Natl Acad Sci U S A. 2009 Aug 4;106(31):12694-9 ; PLoS One. 2009;4(4):e5244 ; Magn Reson Med. 2009 Nov;62(5):1099-105 ; Magn Reson Med. 2009 Nov;62(5):1099-105 ; J Magn Reson Imaging. 2008 Aug;28(2):497-503 ; J Biol Chem. 2008 Jun13;283(24):16342-54 ; J Cereb Blood Flow Metab. 2008 Apr;28(4):712-24 ; Cell Metab. 2007 Jun;5(6):476-87.

➨ **Partner 3 : Molecular Sciences Institute (UMR CNRS 5255), Bio-active molecules and Synthesis Team, E. Fouquet**

The activity of the team is directed towards organic and organometallic chemistry. The challenge is to develop new reactions dealing with practicability, efficiency and speed. Furthermore, we are engaged in developing all these new methodologies in a sustainable way.[9] As a consequence, this chemistry will frequently appeal to metal catalyzed coupling reactions,[1] either in a homogenous[6] or heterogeneous fashion.[10]
The applications of these reactions are then all directed toward Life Sciences and Medicinal Chemistry. They can be focused to the stereoselective synthesis of bioactive molecules,[2,3,4] in order for instance to evidence their interactions with proteins.[5] But they are mainly devoted over recent years to the labeling of small molecules or macromolecules such as peptides and oligonucleotides for TEP Medical Imaging.[7,8]

J. Org. Chem. 2009, 74, 1349-1352 ; **ChemSusChem** 2008, 1, 718-724 ; **Curr. Med. Chem.** 2008, 15, 235-277 ; **Chem. Commun.**, 2006, 97-99 ; **J. Org. Chem.**, 2005, 70, 1953-1956 ; **Biochemistry** 2003, 42, 10385-10395 ; **J. Org. Chem**, 2003, 66, 3693-3712 ; **J. Org. Chem.**, 2001, 66, 6305-6312 ; **Angew. Chem I.E.E.** 2000, 39, 1799-10395 ; **J. Org. Chem.**, 1997, 62, 5242-5245.

➨ **Partner 4 : Cardio-Thoracic Research Center of Bordeaux (U INSERM 1045), Cardiac ElectroPhysiology Team, M. Haïssaguerre**

The Electrophysiology team headed by M Haissaguerre has always been ranked as the best for the treatment of electrophysiological disorders in France. It was the first in the world to introduce catheter ablation therapy for atrial fibrillation over 15 years ago, a therapeutic procedure that is currently part of the international recommendations. The procedure is the most widely performed ablation in Europe/USA, on more than 200 000 patients in 2010. Our group is the most active in catheter ablation, CRT and defibrillation in France.

Michel Haissaguerre

The team has also achieved substantial breakthroughs in understanding sudden cardiac death, outlining the role of early repolarisation in unexplained deaths and the triggering of ventricular fibrillation by the Purkinje tissue. The team has the most experience in mapping of triggers of ventricular fibrillation in the world.

The team has also achieved major breakthroughs in cardiac electrical dysfunction in heart failure and is a co inventor of cardiac resynchronization therapy for drug-refractory heart failure (P Ritter).

The team has been awarded prestigious Louis-Jeantet prize of Medicine in 2010, French Academy des Sciences prize of Medicine in 2010, Mirowski Award Excellence in cardiology in 2009, Boston Award in electrophysiology in 2008, Best European scientist award Gruntzig in 2005, Nylin Swedish Royal society of Medicine in 2004 and others for pivotal inventions in the field of clinical electrophysiology.

***N Engl J Med** 2008 May 8;358(19):2016-23 ; **N Engl J Med** 1998 Sep 3;339(10):659-66 ; **N Engl J Med** 2004 Dec 2;351(23):2373-83 ; **Circulation** 2008 Dec 9;118(24):2498-505 ; **Circulation**1997 Feb 4;95(3):572-6 ; **J Am Coll Cardiol**, 2010. 55(10): p. 1007-16 ; **Circulation**, 2002. 106(19): p. 2479-85 ; **Circulation**, 2006. 113(5): p. 616-25 ; **Lancet**, 2002. 359(9307): p. 677-8 ; **Circulation**, 2000. 101(25): p. 2928-34.*

➨ **Partner** 5 : Cardio-Thoracic Research Center of Bordeaux (U INSERM 1045), Bronchus Remodeling Team, P. Berger

The **bronchial remodeling** team headed by Patrick Berger is recognized as a leading team in Europe in the field of airways diseases. During the last 4 years, the team has identified novels mechanism implied in bronchial remodeling in asthma and has set up new imaging tools to quantitatively estimate airway morphometry in patients. More specifically, our research activities have led to the determination of molecular mechanisms implied in the auto-activation loop smooth muscle cell – mast cell responsible for **mast cell infiltration** and adhesion in asthma, to the identification of calcium-induced **mitochondrial dysfunction** leading to airway remodeling in asthma and to the development of **imaging tools** to assess airway remodeling in vivo using HRCT. Recently, the team has expanded its research field with the recruitment of a senior researcher specialized in **lung MRI**. In summary, during the last 4 years, the team has acquired an internationally recognized and comprehensive expertise in translational research (including cellular and molecular assays, pre-clinical and clinical imaging) for airways diseases.

***Am J Respir Crit Care Med** 1998 , 157: 610-616 ; **Radiology** 2003, 228 (1): 85-94 ; **FASEBJ** 2003, 17 (14) : 2139-2141 ; **J Aller Clin Immunol** 2004, 114 : 66-72 ; **Radiology** 2005 , 235 (3) : 1055-1064 ; Am **J Respir Cell Mol Biol** 2006 , 34 (1) : 49-55 ; **J Immunol** 2006 , 176 (3) : 1860-1868 ; **J Exp Med** 2007 , 204 (13) : 3173-3181 ; **Radiology** 2007, 242 (2) : 563-572 ; **Radiology** 2009 , 253 (3) : 844-853.*

➨ **Partner 6: Neuroscience Imaging Group (UMR CNRS6232), Unit B. Mazoyer**

The Groupe d'Imagerie Neurofonctionnelle (GIN, UMR CEA-CNRS-UB2) has pioneered brain activation studies in France and has contributed to the emergence of cognitive neuroimaging as a research domain at the International level. Over the past 20 years the GIN, using PET first and then FMRI, the GIN has made original contributions in the areas of language, mental imagery, visuo-spatial attention, arithmetic and logic activities, and the conscious resting state. More recently, the GIN has also pioneered the use of large MRI databases in neuroepidemiological research on aging. The GIN has been fully in charge of setting-up and operating the 3T-MRI platform of Cyceron in Caen, and some of its methodologies have been adopted by the international community (its AAL software has so far received over 1,100 citations). GIN research and technical staff have made large contributions to the training of young scientists and technicians in this domain. They have organized an academic course (Master Degree in Neurosciences and Imaging for Health), trained more than 30 PhD's, and organized three summer schools. Since 1990, the GIN has produced 168 peer-reviewed articles that have so far received 8,500 citations. The GIN H-factor is currently at 50.

Circulation 12:1644-50 ; Neuroimage 24:1205-13 ; Neuroimage 30:1414-1432 ; Neurology 70:1601-1607 ; Neuroradiology 54:209-220 ; Brain Research Bulletin 80:133-138 ; Annals of Neurology 65:706-715 ; Neuroimage 53:1064-1069 ; Cerebral Cortex 20:1476-1485 ; Journal of Neuroscience 30:13314-13318.

- **Partner 7 : INCIA CNRS Unit, NeuroFunctional and Cognitive Imaging Team, Team M. Allard**

The team "Cognitive Neuroscience and Neuroimaging" has focused on anatomo-functional substrates of cognitive deficits in neurological disorders. In particular, we have demonstrated an increasing neurotransmitter deficit in the early phases of Alzheimer's disease that is accompanied by a progressive alteration of the posterior fiber track microstructure. In addition, we have demonstrated that the density of gray matter can be correlated with cognitive and educational status of patients.

Neuroimage 24(4):937-47 ; Hum Brain Mapp 26(3):157-69 ; J Cereb Blood Flow Metab 28(9):1624-34 ; Neuroimage 40(1):280-8 ; Hum Brain Mapp 30(4):1133-43 ; Neurology 73(19):1579-83 ; Prog Neuropsychopharmacol Biol Psychiatry 33(4):682-7 ; Neurology 75:1245-48 ; Neurobiol Aging 31(9):1582-92 ; PLoS One 5(7):e11571.

- **Partner 8 : Neurobiology of Myelin Diseases Laboratory (INSERM U1049) Unit K. Petry**

Our research on "***Neuroinflammation, Imaging and Therapy of Multiple Sclerosis***" – MS (creation of new INSERM research unit in 2011) generates **real translational research** from bench to bedside. By developing major **methodological breakthroughs** (innovation of immunochemical and molecular biology techniques, adaptation of methodologies for in vivo studies), we have made major contributions elucidating new **molecular alterations** and **inflammatory mechanisms as essential factors in the development of autoimmunity causing the neurological handicap of MS disease.** In neuro-inflammatory lesion development of both MS patients and experimental animal models

(EAE), we have demonstrated the role of free nitrosative radicals in relation with macrophage inflammatory activity allowing development of clinical MS markers: a) anti-S-NO-cysteine antibodies to predict EAE severity and MS relapses; b) nanobiotechnology for MRI monitoring of monocytes/macrophage brain invasion for prognosis of disease severity and preclinical evaluation of therapeutics; innovation transfer to MS demonstrated the first MRI in vivo spatiotemporal discrepancy between inflammatory macrophage infiltration and the rupture of the blood-brain barrier (BBB); c) developing experimentally a new curative therapeutic approach by administration of immunomodulatory monocytes to suppress severe EAE under MRI control; d) defining both molecular alterations of the BBB and vasogenic oedema formation that were monitored by MRI provided new in vivo information on extra cellular water random motion and macromolecular content; e) defining disturbances of neuronal networks by elucidating the urinary bladder dysfunction as very severe pharmacological neurological deficit and the their restoration; f) defining the alteration of cognitive functions as consequence of pathophysiological MS disease progression inducing new neurological network activation as evaluated by functional MRI, however with limited compensation capacity.

Neurology. *2010 Oct 5;75(14):1241-8 ;* ***Mult Scler***. *2010 Sep 2. [Epub ahead of print]PMID: 20813772 ;* ***Thyroid***. *2009 Dec;19(12):1401-6 ;* ***Bioconjug Chem***. *2009 Nov;20(11):2114-22 ;* ***Neuroimage***. *2009 Aug 15;47(2):659-66 ;* ***Hum Brain Mapp***. *2009 Apr;30(4):1133-43 ;* ***Brain***. *2008 Mar;131(Pt 3):e92. Epub 2007 Oct 25 ;* ***J Physiol***. *2007 Jan 15;578(Pt 2):439-50 ;* ***AJNR Am J Neuroradiol***. *2006 May;27(5):1000-5 ;* ***Neuroimage***. *2006 Aug 1;32(1):266-74.*

↘ Overview of TRAIL teams "excellence"

Since 2005, the LabEx teams have obtained 14 awards (among which: M. Haissaguerre Louis-Jeantet prize of medicine 2010, Boston Award 2008; H. Valeins Cristal CNRS 2007; E. Fouquet IUF Junior Member; B. Mazoyer IUF Senior Member; C. Moonen Antony Bernard Award 2006; V. Dousset Outstanding Teacher Award International Society of Magnetic Resonance in Medicine ISMRM 2008) **and more than 60 grants totaling 27,5 million euros (19 ANRs, 4 PHRCs, 4 Europe grants) for their respective research projects. Our LabEx TRAIL demonstrates that it has the capacity to fund research at approximately 5.2 millions euros per year.**

The eight TRAIL teams leaders and the labex Coordinator have published over 1200 papers which have been cited more than 38 000 times (see table below; only the bibliometry of the group leader is indicated. Source: ISI Web of Knowledge and PubMed).

Researcher	H-index	Total number of papers (PubMed)	Total number of citations	Average annual citation index	Average citation per papers
HAISSAGUERRE Michel	61	426	15120	521	30
MAZOYER Bernard	51	154	8825	284	38
DOUSSET Vincent, Coord.	31	116	3450	218	30
ALLARD Michèle	27	116	1557	40	13
PETRY Klaus	27	72	1206	75	15
BERGER Patrick	17	38	796	61	21
FOUQUET Eric	17	59	754	31	12
FRANCONI Jean-Michel	14	66	418	29	6
Total		**1202**	**38706**		

Exploitation of results

In summary, the LabEx teams have obtained 11 patents (see details in section Annexe 7.4.3) with 2 of which being exploited through license periods. In addition, 2 innovative firms have been established from LabEx team projects.

↘ Regional environment

Healthcare industry in the Aquitaine region encompass 73 companies and subsidiaries (UNEDIC source), and employs over 7800 people. This represents 5% of regional industrial employment as well as 4,3% of employment in national healthcare industry and includes the following sectors.

- Pharmaceutical companies. Around 10 major Pharmaceutical firms are located in Aquitaine (Sanofi-Aventis, BMS/UPSA, Meda, Pierre Fabre…), and they employ over 3000 people, essentially for drug production and industrial development (Source: LEEM). Although strategic decisions are mainly taken in headquarters located in another region or overseas, contacts with regional directors facilitates collaborations of academic labs with these firms.

- Drug development and biotechologies. About 20 biotech and R&D contracting companies (Flamel, Créapharm, Itec services, Mitoprod…), essential for the chain of drug development, are located in our region and employ over 500 workers (Source: LEEM). The skills of these companies include drug activity screening, toxicity assessment, analytical chemistry, galenic formulation, packaging of clinical batches, and regulatory record. These companies have a high innovation potential, and therefore are a main resource for academic/industrial collaborations.

- Medical devices. The medical device industry represents a pool of approximately 1500 jobs, and an important market in the Aquitaine region.

- Medical informatics._Aquitaine region is ranked first for Medical informatics and Medical ICT (Information and Communication Technologies) (Source: DMS Conseil). Medical software leaders (Agfa Healthcare, McKesson France, Siemens Health Services, AGDF Cégédim RS) as well as smaller, fast-growing companies (Imagine Editions/HelloDOC, Sigems, WEB100T...) employ in Aquitaine region around 900 people (source DMS Conseil, 2008). They are currently joining in association to better organize their development and to promote their skills, with the assistance of the Agency Innovalis Aquitaine. Bordeaux hospital (CHU) collaborates with these companies to experiment with new healthcare solutions and software.

- Animal healthcare. A unique but fast-growing veterinary pharmaceutical company is located in Aquitaine region : CEVA Santé Animale. Founded in 1999, CEVA now ranks the ninth largest animal health group in the world. Potential collaborations with academic labs and Bordeaux university hospital (CHU) will likely be developed for pre-clinical assays.

- The Biomaterials and implantable device industry and research laboratories is represented by the 2ACBI Association (Aquitaine Association Biomaterials and Implants). 2ACBI aims to organize and promote this important industry in Aquitaine, which includes the entire chain of

research and development of implantable devices. This association is an important link in the Health Cluster, because it structures the chain of the implantable device. The university labs and the Bordeaux hospital (CHU) services that work on biomaterials are part of this association, and collaborate with industrial members.

- The non-implantable medical device also represents an important part of Aquitaine health industry, with several medium-sized companies (Actéon, Technoflex, Technofluides, B. Braun…).

↘ Structured industry in Aquitaine

A **Healthcare Cluster** is being created in Aquitaine to develop a full value chain for the development of potential innovations up to patient and/or professional care, including actions for enhanced capacity of local clinical investigation and financial valuation by industrial exploitation and job creation. This project is being conducted by Bordeaux University together with the GIPSO, "Groupement Interprofessionnel des industries Pharmaceutiques et de Santé du Sud-Ouest" with the help of 2ADI, Aquitaine Agency for Industrial Development.

Together with the creation of a health cluster, the companies, hospitals and medical professionals involved in clinical investigation in Bordeaux are creating a GIE (Economical Interest Group) called the **Bordeaux Clinical Investigation Group (GBRC).** This groups aims to i) enhance the capacity of local clinical investigation, ii) Improve organizational skills and iii) increase awareness of international firms and Contract Research Organizations (CROs) as well as patients. Hence, this organization will facilitate all the collaborations of academic labs with industrial partners that include clinical investigation.

Our LabEx TRAIL will benefit of all these existing and new organizations that offer multiple connections to the economic world.

Industrial partnerships

Given the obvious benefits for patient health of results in the field of medical imaging, all the partner teams involved have developed strategies to exploit and transfer these results into medical applications. In order to do so, they have developed a network of collaborations with industrial companies, as well as with national and European health organizations and commissions.

Contacts with industrial companies were first initiated by communicating results in scientific meetings, or through publications. Collaborations resulting from these contacts proved benefits for each party, therefore the research teams involved in this project have now developed strong partnerships, and share development programs with these companies.

Industrial applications of the TRAIL medical imaging teams lead to various products, in different industrial sectors:

- Medical imaging device: General Electrics Healthcare, Philips Healthcare, Siemens, Brucker
- Imaging contrast agents: Guerbet Group
- Radiotracers synthesis device: General Electrics Healthcare
- Pharmaceutical Companies: Merck Serono, Novartis

GE-Healthcare

GE Healthcare is a leading manufacturer in medical imaging and information technologies, medical diagnostics, drug discovery and biopharmaceutical manufacturing technologies.

We have built a very strong and mutually profitable partnership with GE Healthcare, to develop novel imaging devices as well as radiopharmaceuticals.

Michèle Allard's lab, "Radiochemicals and TEP research", takes part in the development of a new concept that will be industrialized by GE: the LOTUS platform, which will enable local production of several radiotracers in a short time and with a high specificity. The Allard lab will be the unique site in France to test and validate this platform, together with other international sites. We will develop new pharmaceuticals, perform image processing and analysis after in vivo animal imaging, and validate these new pharmaceuticals for in vivo imaging in animals and humans. Furthermore, the Radiochemicals and TEP research lab is in the process of qualifying for the MDX (Medical Diagnosis) investigator Center label, provided by GE Healthcare together with the French health national agency AFSAPS.

Siemens

Siemens Healthcare is one of the world's largest suppliers in medical imaging, laboratory diagnostics and medical information technology. Siemens is a main partner for the TRAIL LabEx teams. First, our methodology teams develop new imaging sequences in various medical applications (Oncology, Neurology, Cardiology, Pneumology, Nephrology). These novel sequences are then tested for validation by the other teams, by performing pre-clinical studies in their field of application. After this validation, the results can be transferred to Siemens for use in their equipment. Moreover, our teams test and validate new devices developed by Siemens, by performing pre-clinical studies.

The Franconi lab has built a long-term collaboration with Siemens. For instance, they collaborated to develop cellular imaging of brain tumors with nanoparticles. This project was performed with the help of a PhD student on a CIFRE doctoral contract supported by Siemens. Together with the lab members, he developed MRI sequences to visualize and quantify contrast agents in vivo. To facilitate this development, Siemens also offers the use of its proprietary software.

This strong partnership with Siemens is likely to lead to collaboration with the LabEx teams working in the field of cardiology, which is an area of interest for Siemens.

- **Bruker**

Bruker systems cover a broad spectrum of applications in all fields of research and development, including analytical magnetic resonance instruments such as NMR, preclinical MRI and EPR. Worldwide more than 4,000 employees are working at over 90 locations.

Jean-Michel Franconi's lab interacts with Brucker, and helps in developing new MRI sequences for visualizing specific organs and structure by MRI. These newly developed sequences are then integrated in a prototype version by Brucker, which will be tested for validation by performing preclinical studies in one of the TRAIL partner labs (depending on the target organ).

- **Guerbet**

Guerbet's group headquarters are located in France, and represent 1300 employees and 20 affiliates worldwide. Guerbet is a provider of contrast media and imaging solutions for healthcare professionals, used for X-ray imaging, MRI and Nuclear Medicine. It is a leader in France in this market.

Guerbet interacts with multiple teams of the LabEx TRAIL, and provides contrasts agents that are used by our teams for research purposes. For instance, our teams experiment the biodistribution of these contrasts agents by MRI. These results are used by Guerbet to compare with their own biodistribution results obtained with a different approach, in order to show the traceability of their contrast agents and reproducibility of the trials.

- **Philips Healthcare/Medical Systems**

Philips healthcare's headquarters are located in both the Netherlands and the USA. Philips Healthcare develops a large range of healthcare products, including imaging equipment and devices.

Chrit Moonen's lab collaborates with Philips to develop safe and non-invasive methods for MR-guided thermal ablation of malignant tumors of breast, liver and kidney with high intensity focused ultrasound (HIFU). This project requires important technological developments and innovations on both HIFU hardware/software and MRI hardware/software. The development of MR guided HIFU for the treatment of these tumors would represent a major breakthrough.

- **Merck Serono**

Merck Serono's global headquarters are located in Geneva, Switzerland. It is one of the world leaders in the pharmaceutical industry, and develops innovative drugs in multiple therapeutic areas of focus: oncology, neurodegenerative diseases, cardiometabolic care, fertility and endocrinology.

Merck Serono has partnered with Klaus Petry's lab for over 14 years, for the validation of drug effect on Multiple sclerosis, using in vivo imaging for pre-clinical trials. Merck Serono is currently evaluating their interest for thermosensitive markers developed in this lab.

- **Novartis**

Novartis is an international pharmaceutical company; its global headquarters are based in Basel, Switzerland. Novartis developed its own Center for pre-clinical imaging, and collaborates with Roger Marthan's lab for both pre-clinical and clinical trials involving imaging to validate drug development.

As shown by these collaborations with pharmaceutical groups, imaging can be a valuable tool for pre-clinical assessment of drug efficacy: validation of drug targets, and assessment of pharmakinetics and

metabolism. Our LabEx TRAIL aims at further developing such partnerships with pharmaceutical companies including Merck Serono, in the various medical fields of the LabEx.

In order to attest to their collaborations with our teams, several of our industrial partners have acknowledged supporting the TRAIL LabEx, and committing to strong partnerships, officialized by their letters of interest presented in appendices.

↘ Exploitation through spin-offs companies and "Technology Transfer Units"

In addition to exploitation by external industrial resources, creation of spin-off companies by academic community members is one of the major mechanisms to effectively spread scientific and technological knowledge.

- **Image Guided Therapy** (IGT), located in Pessac (Bordeaux, France), was founded in 2001 as a spin-off of Chrit Moonen's lab. This medical device company designs, builds and commercializes innovative tumor treatment devices. IGT develops patient-friendly, non invasive, image guided ablation devices based on focused ultrasound (FUS or HIFU). Their products are developed thanks to recent advanced achieved in the lab.
  IGT has already developed two main solutions: MR guidance for RF ablation procedures and MR guided focused ultrasound ablation devices (MRgFUS).

  In addition to this spin-off company, two projects of the TRAIL LabEx teams already have reached a mature stage in the transfer to industrialization. Given the charge represented by collaborations and service contracting with industrial companies, Technology Transfer Units (Cellules de Tranfert de Technologie) have been created in order to manage these projects. These units are charged with the promotion of the lab expertise and services, and employ engineers and technicians to manage and carry out the projects. The units are managed by the ADERA association. Regarding management of intellectual property of results, Aquitaine Valo is in charge of the collaboration contracting, whereas each Technology Transfer Unit is in charge of service contracting.

- **"RTTech"** is a Technology Transfer Unit that offers expertise and service for developing real-time image treatment software for MRI imaging. This Unit was created in 2010, in order to exploit the results of Chrit Moonen's Lab (UMR CNRS 5231). The strategy of this Unit converges with Philips Healthcare's strategy: Philips faces the heterogeneous needs and demands of its customers in terms of search engine and sophisticated image treatment. The currently available solutions are developed for highly specialized applications and are therefore not flexible enough to accommodate these needs. RTTech offers this flexibility and will fill these industrial needs. Seven patents have been filed to protect this tool and the calculation methods developed in the lab.
  In addition to this strong commercial partnering with Philips Healthcare, the RTTech Technology Transfer Unit aims at developing its business and sign new contracts with further imaging equipment companies.

- **A Technology Transfer Unit** is being mounted as well by Klaus Petry's lab in order to exploit results obtained in the lab and to offer their know-how and services to industrial companies as well as academic labs. It offers:

- Drug testing service for preclinical assays, performed on model animals for multiple sclerosis as well as other types of neuro-inflammation.
- Identification of ligands to be used as specific biomarkers or as nano-cargos for drug targeting. Indeed, the technology developed in the lab to identify tissue-specific ligands can be performed for any application.

- Identification of immunomodulating molecules to be used as core components for the design of new therapeutic drugs. 75 ligands have already been identified and will be offered to industrial partners for co-development.

The last two services are based on a proprietary phage-display subtractive hybridization technology, which is protected by a patent filed in 2010. This technology has a strong competitive advantage on concurrent technologies based on non-specific, massive sequencing followed by informatics analysis of the results. In addition, this technology can be easily performed by a mechanical robot.
This technology has a wide range of applications: all types of inflammations can be potential targets, in particular neurodegenerative diseases such as Alzheimer disease, or even cerebral ischemia. Allergy is another area of applications: specific ligands could be used as a desensitization therapy. The Technology Transfer Unit will prospect in priority companies and labs working in these fields.

Higher education

↘ Existing Training and Education through TRAIL Labex

The main features of the TRAIL Labex concerning education are:

- a significant **education potential** thanks to the 52 university researchers implicated in a broad spectrum of teaching programs, from fundamental disciplines (physics, chemistry, biology biophysics, biochemistry) to clinical diagnosis and therapeutic applications of *in vivo* imaging techniques.
- On the research training level, the number of HDRs represents approximately 60 individuals. In the last four-year contract (2005-2009), this resource permitted the supervision of 63 PhD students and 96 masters students. The work management is also supported by the presence of 21 post-doctoral researchers. It should also be noted that PhD-level research during this period was highly productive from both a scientific and economical view point, including 4 patent applications consecutive to thesis work.

The various education opportunities include:

▶ **Degrees in Science, Engineering and Medicine (University of Bordeaux, Bx1 and Bx2)**

The pan-university education and research organization (i.e. the PRES regrouping the different Universities of Bordeaux) already offers a variety of courses, organized as part of its Licence-Master-Doctoral program. The Masters level within the domain of "Health and Biology" (evaluated A by the AERES) includes specialties such as Bioimaging, Cell Biology and Pathophysiology, Biomaterials, and Neurosciences that propose training in imaging, while the domain of "Drugs and Health products", "Computing", and "Mathematics" also propose relevant training.

At the doctoral level, laboratories involved in the IBIO institute-TRAIL LabEx program belong the Doctoral School "Health and Life Sciences" (evaluated A+ by AERES).

Courses currently available:

- Physics and biophysics initiation in MRI, ultrasounds and PET in Biology of Health undergraduate degree (Licence Degree),
- Biological imaging training as a Masters degree (Biochemistry: physics, chemistry, biology interfaces, cellular Biology and Physiology, and biomaterials (DiMi)
- Imaging in the School of Medicine: basics of MRI, PET, ultrasounds in Licence (first and second year of undergraduate studies), radiology and nuclear medicine in the Masters first and second year (MD degree)
- Imaging at the doctoral school of Bordeaux in Health and Biology (PhD degree)
- Teaching to residents in medicine, surgery, radiology, and nuclear medicine (Specialized medicine degree)

▶ **Non degree education:**

- The Researchers and Professors of Labex TRAIL are involved in many educational initiatives and training programs for continuous education in imaging through diverse international scientific societies (International Society Magnetic Resonance in Medicine, European Network Sonodrug, European Master on Molecular Imaging EMMI, International Davos Course, European Society of Radiology, American Society of Neuroradiology, …), as well as involvement at the national level (workshops concerning knowledge of CNRS, GRAMM (4), JFR (3), GDR STIC health, GDR imagiv, French Society of Radiology, …)
- Teaching at National and International Universities: we are regularly invited to teach in many countries throughout the world: USA (NYU, NIH, …), Japan (Tokyo, Kyoto, Tsukuba, …), England, Germany, The Nederland's, and in many French Universities for various teaching programs (Masters of Neurosciences and Imaging of Health at the university of Caen, Masters of Imaging at the Technological University of Compiegne, DEA, Masters of Imaging and Signals in Medicine at the University Paris 12, Masters of Analytical Chemistry at the university of Nantes).
- The RMSB team (partner 3) is organizing an increasingly well-known annual workshop on MRI technology and physics for 25 applicants. This is a very successful program with applicants coming from several French speaking countries.

▶ **Actions towards the public:** Annual Festival of sciences, Symposiums for high-school pupils, etc

▶ **Didactic articles and book chapters** on *in vivo* imaging techniques: Encyclopaedia Medicalis: 4 articles, 1 in preparation), a chapter in NMR spectrometry in the Biophysics book for 1st year medicine

↘What we want to promote

We need to increase employment-orientated courses in order to prepare students for future job opportunities generated by the bio-imaging field and translational research.

- In this respect we are organizing inter- and multi-disciplinary education with new programs and new degrees:
  - A new INTERNATIONAL BIO-IMAGING MASTER: This masters degree will be taught in English and available to European and International students (starting September 2011, ranked A by the AERES and authorized by the French ministry of higher education)
  - a new PhD program in the Doctoral School oriented toward Imaging and Translational medicine
- Among other initiatives, the TRAIL LabEX project will help by :
  - Offering educational grants and student stipends (see section 6.2)
  - Initiating a new governing organization that will allow building a single showcase of teaching and educational programs
  - Increasing communication about our educational programs (Internet Web site)
  - Encouraging new creative initiatives for appropriate curriculums such as continuing education
  - Reporting to government boards and the general population

Organisation

From 2007 to 2009, the CNRS and INSERM research institutes, the University Victor Segalen Bordeaux 2 and the University Hospital of Bordeaux encouraged the creation of an **Institute of Bio-Imaging** for living animals and humans (**IBIO**). The goals were to increase the visibility of talented imaging laboratories aimed at research spanning from methodology to clinical applications and to attract new teams and world-class scientific leaders. IBIO has been awarded by national and local governmental CPER a grant of 12 Million euros for acquiring new devices (PET for human research, MRI 7T for small animals) and for building an up-to-date facility of 3000 m2 for MRI research, biology and medical applications at the University Hospital.

Existing collaborations

Highlights:

The LabEx teams have been working together for several years. Since 2005, 16 intra-LabEx collaborations have been carried out, leading to at least 40 publications.

The LabEx teams have been involved in 18 national and 17 international collaborations (with India, USA, Germany, The Netherlands), and have developed 21 collaborations with private companies such as GE Healthcare, Philips Healthcare, Merck-Serono, Guerbet, CISbio International, Demptos SA, Toshiba, Siemens, Medtronic.

04/

Technical and scientific description of the project

State of the art

Effective **transfer** of new knowledge, mechanisms, and techniques generated by advances in basic science research to new approaches for the prevention, diagnosis, and treatment of disease is essential for improving health. This first step of translational research (T1) refers to the "bench to bedside" phase that leads to the first testing in humans. It should ideally be followed by the transfer of results from clinical studies to everyday clinical practice and health decision making (T2) [1].
However the process is rarely that simple. The bench to bedside enterprise occasionally yields breakthroughs that in themselves markedly improve diagnosis, prognosis or patient therapies and interventions. Furthermore, the medical environment is rapidly changing: the costs of patient treatment and care are increasing, the budget crisis has decreased health spending, diseases are becoming increasingly chronic with patients being treated over much longer periods of time (cancer, cardiac and neurological diseases, …), the population is aging, and "personalized medicine" for individual patients is increasingly encouraged.
To meet these challenges, the European Commission, the French National Research Institutes and the NIH in the US have made **translational research a priority**, encouraging and developing centres for translational research (60 in the USA by 2012) that take into account all the problems and pitfalls involved in turning new knowledge into clinical practice [2].

Non- or minimally-invasive **imaging technologies** are providing researchers with exciting new opportunities to study animal models and human diseases. With continued improvements in instrumentation, identification of better imaging targets and better-designed imaging probes using innovative chemistry, imaging technologies promise to play increasingly important roles in disease diagnosis and therapy. Nevertheless, improving patient care while controlling expenditures remains a major goal. Although imaging techniques are technologically expensive, they may become one of the methods of choice whose "charter" could be described as follows:

- Improving diagnosis through *in vivo* characterization of the cellular and molecular mechanisms of disease in individual patients
- Monitoring treatments or target delivery of therapeutic agents and performing longitudinal evaluation of targeted therapies
- Interventional imaging procedures as alternatives to surgery and radiotherapy, and for targeting delivery of therapeutic agents or gene expression
- Serving as surrogate markers of drug efficacy for clinical trials
- Personalizing patient care
- Exploring populations to better understand diseases
- Attracting medical industries to create health, wealth and employment

↘ Improving diagnosis by in vivo detection and characterization of the cellular and molecular mechanisms of disease in individual patients

Key words: instrumentation, high fields MRI, PET, PET/CT/MRI multimodality, optical imaging, tracers and contrast agents, biological targets, cellular imaging, molecular imaging, interdisciplinary work.

Several articles have reviewed the enormous potential of *in vivo* imaging techniques only 20 to 30 years old, such as Magnetic Resonance Imaging and Positron Emission Tomography applied for biological, pre-clinical and clinical imaging [3-6]. Optical Imaging is also a newly developing technique that may quickly take into account living animals and, in a near future, humans imaging. Here we want to emphasize the stratification of *in vivo* imaging with magnetic resonance imaging (MRI), positron emission spectroscopy (PET) and optical imaging (OI) from organ to molecules, considering current progresses and requirements for improving the accuracy of diagnosis for better patient care [7,8]. Going from the visualization of an organ and an abnormal tissue to an *in vivo* personalised characterization of metabolism, abnormal cells and specific molecules is a major challenge [9]. For example, higher fields for MRI contribute to increasing the anatomic resolution that is becoming closer and closer to that of the microscope. Multimodality for PET imaging allows a better localization of cancers cells spread in the entire body and provide new observations of cell metabolism by specific tracers targeting active biomarkers [10].

The twenty first century has witnessed an explosion of molecular biology techniques, amazing advances in imaging, and the design of unique imaging probes. Despite the tremendous strides made in these areas of science, the cure for many diseases remains beyond our grasp.
MRI: Molecular and cellular MRI has recently emerged as a novel technology for the noninvasive assessment of biologic processes in living organisms and has substantially progressed in the past few years. The possibility of tracking the survival, migration, and differentiation of cells in vivo, and the ability to monitor metabolic changes or particular gene or protein expression in living subjects, is becoming not only of great interest to scientists investigating fundamental aspects of diseases but also is now finding a translation into clinical settings.
PET: PET permits the mapping and measuring of the rate of physiologic, biochemical, and molecular processes. Therefore, PET has become essential for investigating basic chemical and functional processes in molecular biology. PET plays an important role in molecular imaging and has been used in oncologic diagnosis and evaluation of therapeutic response. In addition, the precise characterization of brain and myocardial tissue enables risk stratification and treatment strategizing for various cerebral and myocardial diseases [11].
In vivo optical imaging: OI is a scan technique that permits visualization of biological events non-invasively in live laboratory animals. Animal models of disease can be monitored by means of fluorescence (FLI) or bioluminescence (BLI) reporters. In vivo optical imaging in the mouse and rat is popular in preclinical drug discovery and can evaluate drug efficacy, pharmacodynamics, pharmacokinetics and biodistribution, a useful tool for translational research.

The interdisciplinary nature of the field mandates a constant dialogue among molecular and cellular biology, chemistry, physics, image analysis, and drug discovery to develop and translate promising approaches into reliable scientific applications and viable clinical diagnostic tools. Furthermore, the rapid evolution of the multidisciplinary approaches of the imaging techniques should be encourage to improve educational programs with the goal of offering a new generation of scientists, engineers and industries' specialists strong skills in bio-imaging technologies combined with basic sciences, biology and medical knowledge.

↘ Monitoring treatments and performing longitudinal evaluation of therapies

Key Words: Imaging and Therapy

A key goal of TRAIL is to improve disease identification, and moreover to better characterize the disease by means of specific biological markers [12]. The more accurate the characterization, the better the evaluation of disease progression and therapeutic decision. The concept of patient care decision-making based on evaluation of treatment efficacy by imaging techniques has been used empirically for decades, especially for cancer. However, the increased choice in treatments, the increasing costs of new drugs and their related deleterious side effects call for targeting treatment to the right population. At the intersection between treatment and diagnosis, interest has grown in combining both paradigms into clinically effective formulations [13]. This concept, recently coined as theranostics, is highly relevant to agents that target molecular biomarkers of disease and is expected to contribute to personalized medicine. It is composed of three steps: 1) selection: using biological and/or imaging markers to select patients that might be responsive to a chosen therapy; 2) monitoring the treatment; and 3) evaluation of the treatment over time. In this respect, MRI and PET multi-modalities are the techniques of choice for disease and therapy management [14]. Although development of imaging technology has strikingly increased in the past decades, **many more sophisticated probes and bio-imaging markers are needed to improve the selection and evaluation of different treatments** [3, 13]. For an example, anti-angiogenic therapies evaluation may benefit from: 1) new technique and new sequences of perfusion and permeability imaging; as well as 2) accurate imaging probes (tracers or specific contrast agents) that specifically target molecules (genes or proteins) responsible for angiogenesis. A personalized theranostic agent would be more accurate in the selection of patients who may respond to treatment, and in assessing the outcome of therapeutic response.

↘ Interventional imaging procedures as alternatives to surgery and radiotherapy, and for targeting delivery of therapeutic agents or gene expression

Key words: Image guided therapy, interventional MRI (iMRI), Drug delivery under imaging control

Mini-invasive procedures are increasingly used as an alternative to surgery. In the past fifteen years, improvements in image-guided therapy have offered patients and physicians new and efficient treatments with increased safety and shorter hospitalization time. For example, tissue ablation by radiofrequency procedures under CT is increasingly used as an alternative to lung or liver surgery in the case of metastases. However, MRI offers a much better controlled procedure with a real-time measurement of temperature and a detailed approach concerning tissue destruction volume [14]. Interventional MRI is under development in helping the monitoring of surgery or proposing alternative treatment. With a concept-based radiotherapy, combining high intensity focused ultrasounds (HIFU) in clinical MRI scanners make it possible to increase the local temperature and induce thermo-destruction of targeted tissues such as uterine myomas, breast cancer or prostate cancer. This concept of using HIFU under MRI control can be extended to drug delivery and to control gene expression [15]. Thermo-sensitive medicines or gene promoters may be engineered in order to be delivered or expressed in time and space, and controlled by the local delivery of heat through HIFU. However, improvement of this technique, testing of drugs and genes promoters, needs to transfer between pre-clinical studies and human in a strong multi-disciplinary environment.

↘ Serving as surrogate marker of drug efficacy for pre-clinical and clinical trials

Key words: New therapies, drug development, bio-markers, Phase II trials

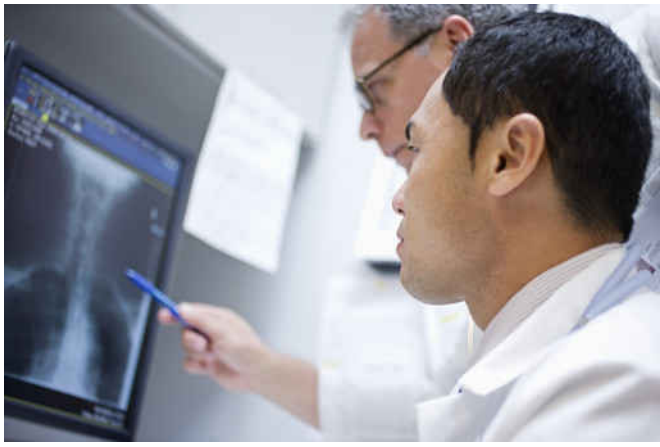
Establishing pharmacologic audit trials provide a means to assess and manage risk in a drug development program and thus increase the rationality of the decision-making process. Using modern technology platforms such as genomics, proteomics, circulating tumor cells and functional and molecular imaging may **improve the success rate and speed of drug development** [16,17]. These platforms also permit examination of the consequences of therapeutic interventions and provide unique insight into human disease biology. In this respect, early clinical trials represent a crucial bridge between preclinical drug discovery and the resource-intense randomized phase III trial-the definitive regulatory hurdle for drug approval. High attrition rates and rising costs juxtaposed to the promise of personalized medicine call for new approaches in the conduct and design of phase I/II trials [18]. Critical to development of new therapies is the ability to detect clinical or pathological change over time. The vast number of novel targeted therapies available for testing dictates that a more efficient system aimed at identifying promising agents for phase III testing needs to be developed. The large number of negative phase III trials over the last several years has renewed interest in refining phase II clinical trials to maximize the chances of success in phase III testing. Thus, incorporation of bio-imaging markers into phase II trial design could allow for more accurate identification of patients who will benefit from targeted therapies [19-21].

Accurate preclinical models are important for pharmacokinetic-pharmacodynamic-efficacy modelling and biomarker validation. At a pre-clinical stage, **imaging techniques enable** the comprehensive characterization of therapeutic interventions and can be used in pharmacokinetic studies, dose-finding studies, and proof-of-concept studies. The growing use of molecular imaging is also helping to control and monitor dosage for increased safety and effectiveness. Thus, molecular imaging techniques may play a **major role in the development of novel therapies** since they measure target expressions as well as function, pathway activities, and cell dispersion in the intact organism [19]. To be maximally useful at an early stage, these bio-imaging markers must be in place before the commencement of phase I trials. Validation and qualification of biomarkers then continues through clinical development. With these technologies already having an impact in the clinic today, additional future advances will come from the application of network analysis to clinical trials, leading to individualized systems-based medicine. For this reason, development of surrogate biomarkers that identify significant disease-associated changes are necessary to expedite treatment development. As an example, recent evidence in Alzheimer's disease demonstrates that imaging may provide more sensitive, and earlier, measures of disease progression than traditional clinical measures for powering clinical drug trials for this condition [20,21]. Magnetic resonance imaging, fluorodeoxyglucose positron emission tomography, new amyloid imaging techniques, and spinal fluid markers of AD all have great potential to provide surrogate endpoint measures for AD pathology. In addition, current development focuses on novel technologies using positron emission tomography to directly image the neuritic plaques and neurofibrillary tangles of AD in order to provide more specific measures of disease progression in future clinical trials [20].

↘ Personalizing patient care

Key words: personalized medicine, modelling

We currently rely on large randomized controlled trials and meta-analyses to make clinical decisions; this places us at a risk of discarding subgroup or individual-specific treatment options due to their failure to prove efficacious across entire populations. Currently, while non-image based clinical outcome metrics include morphology, clinical and laboratory parameters, these are obtained relatively late following treatment. There is a new era emerging in personalized medicine identifying genes, endophenotypes, and biomarkers of disease that will facilitate diagnosis and predict treatment outcome [22]. We are at the threshold of being able to predict individual treatment response, primarily through genetics and imaging [23].



↘Exploring populations to better understand diseases

Key words: cohorts, epidemiology, MRI bio-imaging markers, quality

The interest of developing population-based studies in several medical fields is evident for increasing our knowledge of epidemiology and for practical decision-making at a population level [24]. Population neuroscience can be used to evaluate the presence or absence of causality in associations discovered by observational studies. However, despite technical developments of computerization and increases in the number of MRI devices in past decades, only a few population-based studies have been carried out with MRI as an additional sensitive marker. There are several challenges to population-based studies with MRI, including quality assurance, quality control and intersite coordination. In Bordeaux, the Institute of Public Health (ISPED), a collaborator of our TRAIL (see list of collaboration Pr Dartigues/Dr Tzourio and CIC-Epidemiologie Clinique 7) has been developing for more than 20 years large-scale population-based studies on neurological diseases (PAQUID, …).

↘Attracting medical industries to create health, wealth and employment

Key words: socio-economics, medical-economics, cost savings

Technological breakthroughs in diagnostic imaging modalities as well as progress in interventional procedures have brought medical imaging to assume a role as the most important diagnostic modality as well as the forerunner of minimally-invasive, image-guided surgery. However, as healthcare expenditure is increasing, societies and governments become increasingly cost-conscious. On the other hand, as imaging techniques facilitate more timely and precise diagnoses, it has become the most important guide to optimizing therapeutic decisions. By shortening patients' recovery and speeding return to normal life, imaging techniques prove to be highly cost saving. Furthermore, modern imaging procedures eliminate the need for more invasive and thus more costly outmoded diagnostic approaches, leading to an additional decrease of health care expenditures.

Objectives of the project compared to the state of the art and in relation to the SNRI

↘ Scientific programme

This section is organized as follows

- **Concept and General Objectives of TRAIL LabEx Scientific Project**

  Introduction

  → General Presentation of IBIO and TRAIL LabEx: a dynamical process for T1 and T2 translational research as well as for international visibility and attractiveness

  → Presentation of basic and clinical research – Interactions between work packages and clinical research applications in the medical fields

  → Means for Research

  1. Buildings
  2. Imaging Device Platform
  3. Collaborations for developing research
  4. Support services for translational research

  → The roadmap for TRAIL LabEx

  5. Six top goals for the next ten years
  6. Solutions from the TRAIL LabEx

- **Scientific Project in Detail**

  - Presentation in detail of the 7 Imaging Research Work Packages
  - Presentation in detail of the 5 Clinical Research Applications in the medical fields

- **Epidemiology and medico-economics – the public health impact analysis of our translational T2 research**

Concept and General Objectives of LabEx TRAIL Scientific Project

Introduction

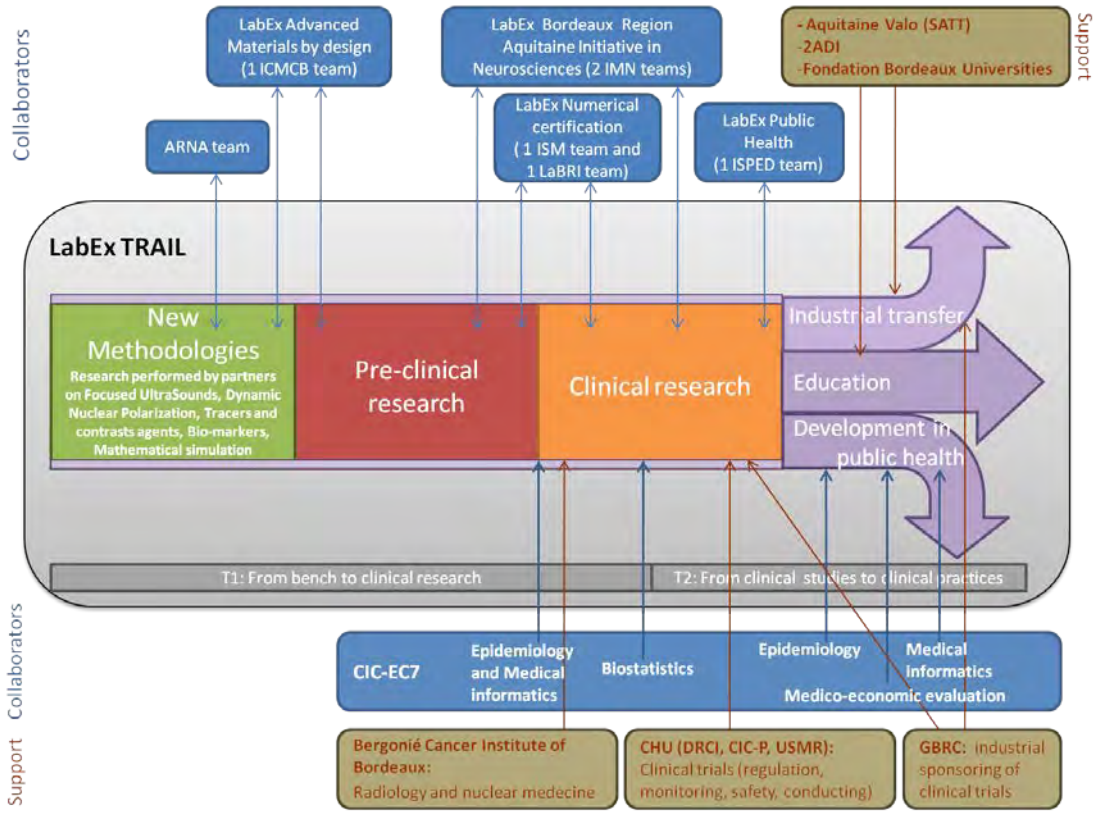
Health, well-being, nutrition and biotechnologies are the first priorities of the "Stratégie Nationale de Recherche et d'Innovation" (SNRI).

The state-of-art description presented in section 5.1, reassesses many of the issues that are facing modern medical imaging. *In vivo* imaging is no longer a question only of "technology": it is an interface of several disciplines that must work together in order to move forward knowledge, patient care and public health. Furthermore, despite current hopes, the transfer of research from basic science to the medical field is increasingly tedious and disappointments or failures are common. In particular, building connections between the research world and that of industry is increasingly difficult, with the former looking for rapid human applications while the later grapples with the heavy burden of investment and lengthy development procedures. We have to oversize our partnership with private companies to a common thinking, to build the research and educational programmes together, and evaluating together the potential of the research products for public health.

The Bordeaux TRAIL initiative is capable of responding to fundamental needs in the partnerships that should exist between research, industry, education and health. We are putting together excellent scientists from diverse origins (e.g. physicists, chemists, biologists, mathematicians, engineers, physicians, teachers), in order to build an interdisciplinary Institute of Bio-Imaging (named IBIO) of nearly 200 individuals. **One of our strengths** is the interconnection between research (all teams belonging to CNRS, INSERM or CNRS-CEA) and clinical applications due to the close proximity (intellectual and physical) of one of the top French bio-medical universities (Université de Bordeaux Bx2), one of the best and largest French University Hospitals (CHU de Bordeaux) and a top French Cancer Institute (Institut Bergonié). **Based on seven specific research topics (referred to as Work Packages)** that are applied to major medical fields including oncology, neurology, cardiology, pneumology and nephrology, the strategy proposed relies on a proactive organization that helps researchers, clinicians and industrials to resolve health problems through improved knowledge transfer. This structure will carefully harmonize the research teams while keeping their independent skills, attractiveness and competitiveness.

Furthermore, it will use **collaborative research units** outside the IBIO in order to promote and evaluate the translational research to both patient care and socio-economics in cooperation with the Public Health Institute of Bordeaux (INSERM Centre of Clinical Investigation-Epidemiology). The clinical research process is ensured by several **institutional support structures** that are well-identified and that promote high quality of work.

The TRAIL Scheme for Operating Translational Research



Another strength relies on the international recognition of local talent and their high quality of work in the field of bio-imaging, explaining why the IBIO Institute and its TRAIL project is strongly encouraged and supported by the University of Bordeaux, National Research Institutes such as the CNRS and INSERM, local regional government and the ministry of research and higher education.

We have also identified **several weaknesses** that the present initiative should help resolve in order to become a world-class research Institute. Thus, in our roadmap for the next 10 years, we have ranked 6 TOP GOALS presented below that will tackle these weaknesses. The funds of TRAIL project will have a direct effect on addressing these goals and building the Institute IBIO through their allocation to research, education, governance, development with industrial partners and research on socio-economics effects. One of the principles for awarding funds will be evaluation of projects based on grant calls promoted by the TRAIL LabEx.

➘General Presentation of IBIO and LabEx TRAIL: a dynamical process for T1 and T2 translational research and for international attractiveness

From 2007 to 2009, the CNRS and INSERM research institutes, the University Victor Segalen Bordeaux 2 and the University Hospital of Bordeaux encouraged the creation of an Institute of Bio-Imaging for living animals and humans (IBIO). The goals were to increase the visibility of talented imaging laboratories aimed at research spanning from methodology to clinical applications and to attract new teams and world-class scientific leaders. IBIO has been awarded by national and local governmental CPER a grant of 12 Million euros for acquiring new devices (PET for human research, MRI 7T for small animals) and for building an up-to-date facility of 3000 m2 for MRI research, biology and medical applications at the University Hospital. A research leader in lung imaging has also joined IBIO in September 2010, and a new internationally-recognized team composed of 12 researchers in neuro-imaging (CNRS-CEA B. Mazoyer, formerly from Caen) will being joining the IBIO in 2011.

IBIO has been designed to gather excellent resources around translational research in imaging. However, its development requires more substantial means.

Our TRAIL Lab aims to combine state-of-the-art imaging capabilities with powerful molecular biology techniques to define strategies with 'intent to cure'. We are building a human resources network within TRAIL and are creating through international collaborations a new organization consisting of a multidisciplinary group of top scientists focused on translating molecular capabilities into imaging possibilities with the purpose of understanding, diagnosing and curing medical conditions. Nearly all of the investigators participating in this TRAIL Lab have interactive collaborative projects with one or more of the other investigators. The synergism generated by the collective skills of this unique group will lead to significant advances in the understanding of cancer, neurologic, cardiac, bronchial and kidney diseases and their treatments. The research components utilize MR, PET and Optical Imaging technology to understand, diagnose, predict and treat. We have selected developmental highly relevant and interactive projects. Four basic science resources devoted to: i) physics; ii) molecular and cellular biology; iii) imaging probes, tracers and contrast agents; and iv) mathematical simulation and modelling in order to provide the infrastructure to support the pre-clinical research activities. Translation from pre-clinical to clinical research will be organised by a single, original and unique process made possible by the high quality of clinical research organization provided by the Bordeaux University together with the University Hospital, the Cancer Institute of Bordeaux and the Research Institutes (CNRS, INSERM, CEA, INRIA). For industrials and manufacturers, we will provide a one-stop service that will allow mutual understanding and solutions at all steps of the research process. In addition, we will provide an evaluation of the socio-economic impact of our research with the help of a dedicated team from the Public Health Institute of Bordeaux. An educational program will train the bio-imaging specialists of the future with a special emphasis on multi and inter-disciplinary education.

➘Presentation of basic and clinical research – Interactions between work packages and clinical applications

We defined 7 WPs according to recognized excellence (5 WPs) and two emerging and original risk-taking topics (2 WPsR*):

WP1: MR Guided High Intensity Focused Ultra Sounds
B Quesson CNRS / UB2
To further develop MRI guided High Intensity Focused Ultrasound towards treatment of tumors in particular for liver and kidney, as well as breast and prostate from large animals to clinical trials.
Objectives: 1) The development of MRI guided HIFU for thermo-ablation of cancer in liver and kidney, as well as breast, and prostate from large animals to clinical trials; 2) The development of MRI guided HIFU for image guided drug delivery to achieve a) local release of drugs from circulating nanocarriers, b) extravasation of drugs, c) crossing natural barriers such as cell membranes, blood-brain-barrier.

WP2: New MRI Contrasts – New MRI Sequences
JM Franconi UB2/CNRS - S Miraux CNRS/UB2
To increase spatial and temporal resolutions, increase sensitivity, increase specificity to become more quantitative and to adapt NMR/MRI to systems biology.
Objectives: The effort will be focused on the development on 3D, real-time and whole body sequences for morphological, functional and molecular and cellular MRI. Three main and interconnected steps: sequences design and implantation, preclinical evaluation on small animals and transfer to clinical research and applications.

WP3R*: Dynamic Nuclear Polarization
JM Franconi UB2/CNRS - E Thiaudière UB2/CNRS
A risk-taking breakthrough research of new Targeted DNP-Contrast Enhanced MRI for diagnosis through protease spotting.
Objective: to use dynamic nuclear polarization and specific free-radical-based contrast agent to target disease-associated protease activities.

WP4: Radiopharmaceutical Tracers and Contrasts Agents
E Fouquet CNRS / UB1 - M Allard UB2 /CNRS/CHU
To create responsive agents for molecular imaging, using different imaging modalities towards functional imaging (MR, PET and Optical)

WP5: Targeted Biological Markers for Bio-Imaging
KG Petry INSERM/UB2
The imaging biomarkers serve in prediction of patients at risk, in diagnosis of patients, in evaluation of disease progression, in disease prognosis and in evaluation of therapeutic interventions-
Objective: Two major strategies: 1) The tropism of cellular infiltration (macrophages, T cells, mesenchymal stem cells); 2) The molecular alterations of endothelial cells recognized by specific ligands

WP6R*: Mathematical Simulation and Modelling
J Palussiere CLCC/CNRS - P Jaïs UB2/INSERM/CHU
To compute patient-specific digital models from multimodal imaging data in order to reproduce diseases and treatments in silico.
Objectives: To understand pathophysiology, to predict spontaneous outcome, to compare treatment strategies.

WP7: Structural/functional neuroimaging tools for preclinical, clinical and population studies
B. Mazoyer CNRS/CEA/UB2
Objective: implement a structural/functional MRI (3T/7T) neuroimaging platform fields dedicated to translational research in the field of age-related disorders and neurodegenerative diseases.

UB2: University Bordeaux 2; UB1: University Bordeaux 1; CHU: University Hospital; CLCC: Cancer Institute

WP8: Translational methodology
P Perez INSERM/UB2

UB2: University Bordeaux 2; UB1: University Bordeaux 1; CHU: University Hospital; CLCC: Cancer Institute

The five TRAIL Medicine-Applied Translational Research Imaging Fields of Excellence:

The development of each WP fosters the development of translational research with imaging specialties. Our choice takes into account the existing excellence of research in those particular fields as attested by rate of publications, patents, evaluations from national research agencies, international attractiveness, etc.

- **Oncology -** We will develop our researches for the translation on cancer research with 1) new radiopharmateucicals as aptamers and peptides; 2) mathematical models applied to solid tumors; 3) image-guided therapy to treat patients (bone, uterus, liver, breast).

- **Neurology -** Neuroimaging research will address two major issues: 1) the development of diagnostic and therapeutic tools for neurodegenerative and neuroinflammation disorders; 2) the identification of risk factors and biomarkers of normal/pathological aging using population cognitive neuroimaging.

- **Cardiology -** The scientific project will focus on the following themes: ischemic cardiomyopathy, heart failure and arrhythmias with new approaches for understanding heart diseases and interventional MRI with intend to treat patients.

- **Pneumology -** To understand, treat and evaluate the bronchial remodelling, hallmark of chronic respiratory diseases we will develop functional CT and MRI including high fields and will focus on evaluation of treatment in asthma and COPD.

- **Nephrology -** Our tasks are to validate functional MR imaging methods for non-invasive renal function evaluation, and new imaging biomarkers of intrarenal structural changes, from inflammation to progressive development of fibrosis.

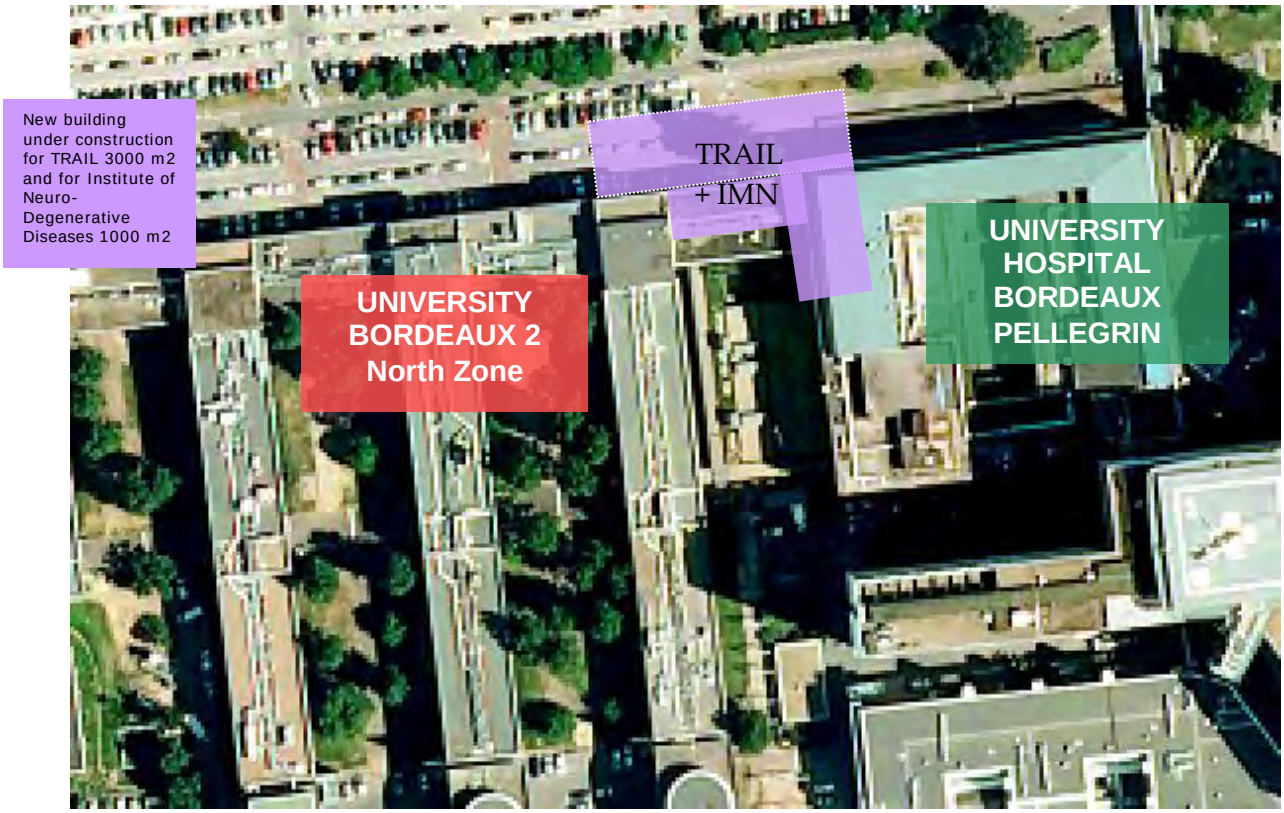
Interactive Researches for Translational Research between WP and Applied Medical Fields

	WP1 MRI guided HIFU	WP2 New Contrast / New Sequences	WP3 DNP	WP4 Tracers and Contrast Agents	WP5 Biological Bio-Imaging Markers	WP6 Mathematic Simulation and Modelling	WP 7 Methodology Neuro-Imaging	WP8 Translational methods
Oncology J Palussière Ph Fernandez C Moonen F Couillaud H Trillaud	Interventional MRI and thermotherapy for drug delivery and control gene expression		Tumor Metabolism	Tumor Metabolism	Tumor Molecular Imaging	Tumor growth modelling		
Neurology B Mazoyer M Allard V Dousset B Hiba		Aging brain		Functional PET Imaging Aging brain	Inflammation Imaging		Functional MRI Cohorts	
Cardiology M Haissaguerre P Jaïs B Quesson H Cochet	Interventional MRI for cardiac ablation	3D coronary velocity mapping		Cardiac Purkinje Network Targeting		Modeling of cardiac electrical disorders		
Pneumology P Berger F Laurent Y Crémilleux		Bronchial wall Imaging	Metabolic and molecular imaging		Inflammation Imaging			
Nephrology N Grenier B Denis de Senneville Ph Fernandez		Kidneys Functional MRI			Inflammation Imaging and Fibrosis			

➘Means for Research

Buildings

The IBIO facilities totalize 7500 m² with a main **3000 m²** new modern and interactive building under construction (opening 1° semester of 2013) at the intersection between the University and Hospital for pre-clinical large animal and clinical translational research imaging. The construction is supported by a National and Aquitaine Region program (CPER) of 8 M euros.



A world-class platform of today and tomorrow

The existing MRI platform « Imagerie et spectrométrie RMN *in vivo* » (PFSI) was recognized first as RIO and subsequently as IBiSA technological platform (see www.pfsi.u-bordeaux2.fr) and is located on a single site (Université Victor Segalen Bordeaux 2, Campus Carreire). Its IBiSA label was renewed in 2010. This platform was founded by two laboratories, the UMR 5536 and the UMR 5231 that perform technological development studies in the field of NMR Imaging and Spectroscopy. The equipment of both laboratories is complementary with the UMR 5536 specializing in small animal studies, and UMR 5231 in human studies. Both laboratories have distinct financial management and direction of their imaging platform.

We have also installed a platform of in vivo optical imaging for small animals including bioluminescence (BLI), fluorescence (FRI), intravital fluorescence (IVM) and fluorescence molecular tomography (FMT) that will function as part of the platform PFSI. This allowed evaluating transcriptional and post-transcriptional dysregulations during the oncogenic process within brain tumors. Original developments were also conducted for demonstrating the feasibility of in vivo control of transgene expression using thermosensitive promoters and MRI-guidance. We are among world leaders in that field. We also developed, in collaboration with CEA-LETI, an original and unique system of bi-functional, optical-US, system for detection of prostate cancer (ANR 07). The next step will be to end-up with endorectal prototypes to be tested on tumor models in small, then big, animals before first clinical testing.

Pre-Clinical Small Animal Imaging Systems for Research Only
Imaging Systems for Research Only
Imaging Systems for Clinical Research and Clinical Imaging

Small Animal imaging and Spectroscopy Research RMSB UMR 5536	Siemens Open Viva 0.2T	Bruker Biospec 4.7T	*Coming 2011* Small animal 7T MR system	Bruker Avance spectrometer/ imaging system 400MHz	Bruker Avance spectrometer 500MHz
Human and pre-clinical Molecular and Functional Imaging Research UMS3428	1.5T Philips MRI system	3T Philips MRI system	In Vivo Optical Imaging Systems		

Located in the University Hospital and in the Cancer Institute are several PET and MRI scanners that provide all the technical, human, and quality insurance suitable for driving clinical research on patients.

Human Clinical Research MRI University Hospital Bordeaux	PET/CT General Electric Research Imaging System	4 x 1.5T Siemens (2) and Philips (2) Clinical Systems – One system with HIFU	*Coming 2011* 3T MR imaging system for ½ time clinical research	**Human Clinical Research MRI CLCC Bergonié**	1.5T Philips Clinical System with HIFU

To develop a state-of-art imaging platform suited for our workpackages, we have responded at several "Investissements d'avenir" grant calls (see section 2 for more details):

Pre-clinical and clinical Equipts Calls for projects "Investissements d'Avenir"	EquipEx 2010 Micro-Cyclotron + microPET/SPECT/CT **For WP4, WP5**	EquipEx 2010 3.0T Interventional MR in cardiac imaging **For WP1, WP6**	Infrastructure Nationale 2010 7TClinical MMRI system **For WP7**	Infrastructure Nationale 2010 Pre-clinical animal 7T MRI for translational R. **For WP2, WP4, WP5, WP7**	*EquipEx 2011* Dynamic Nuclear Polarized MR system **For WP3**

Collaborations for developing research

To achieve our research, we are working with **collaborators** defined as major research teams of the partners with whom collaboration is essential to develop translational imaging research.

- Centre of Clinical Investigation in clinical Epidemiology CIC-EC7 INSERM – Bordeaux 2 University – Bordeaux University Hospital / Bergonié Cancer Institute (AERES A)
- Labo ARNA (*RNA:Natural and Artificial Regulations*) (AERESA+); team "Small RNAs and Aptamers"
- Institut de Mathématiques de Bordeaux et INRIA MC2 (AERES A+)
- Laboratoire Bordelais de Recherche en Informatique (AERES A+)
- ICMCB-CNRS UPR 9048 (AERES A+)
- Institut Maladies Neurodégénératives (AERES A)
- Epidemiology and Bio-Statistics INSERM/ISPED/UB2 (AERES A)
- Laboratoire Biomatériaux et Ingénierie Tissulaire Inserm U577 (AERES A)
- Chemistry and Biology of Membrane and Nano-Objects CNRS UMR 5248, University of Bordeaux 1, University of Bordeaux 2 (Aeres A+)

Support services for translational research

To develop our research, the TRAIL will be supported by several organizations and structures that allow and foster basic research, clinical research or valorization.

- CHU de Bordeaux, including DRCI, CIC-P, Clinical research Unit (USMR) University Hospital Bordeaux
- Bergonié Cancer Institute of Bordeaux
- Groupement Bordeaux Recherche Clinique
- 2ADI (Agence Développement et Innovation Aquitaine)
- Aquitaine Valo (SATT)
- Foundation Bordeaux Universities

➘The Road-Map of TRAIL LabEx

Six top goals for the next ten years

(Top 1) To enforce our fundamental imaging science
We have determined seven work packages that will be applied to five medical fields. The several partners of TRAIL are working with several collaborators from the Bordeaux University.

(Top 2) To reduce obstacles to translational research (T1) from bench to bedside
We will move our research forward to the clinical applications. This will be possible with the organization of several support services that exist in the Bordeaux environment of TRAIL. In addition, we aim at evaluating the clinical impact and the decision-making approach of our research.

(Top 3) To study the impact of our research (T2), new methods and new imaging technologies on clinical trials, personalized medicine, patient care, epidemiology and socio-economic impact
We will design and generate clinical development plans for the innovating imaging techniques; collaborate with support structures in the design and implementation of clinical studies for the aspects of design, biostatistics, data management, statistical and medico-economic analysis and valorization; develop innovative designs and statistical methods relevant to the clinical aims of the studies and the nature of data provided by the new imaging techniques.

(Top 4) To provide a one-stop solution and showcase promoting relationships with industrial partners in the vicinity of Bordeaux as well as on a national and international level (e.g. with General Electric, Siemens, Philips)
Although IBIO is in association with several industrial partnerships, we want to attract more large industrial companies, as well as small emerging companies to develop reciprocal interest saround imaging and medically applied research. We will develop a single and simple organization that will simplify the industrial relationships. We will benefit from the know-how of industrial partners and they will benefit from integrated research from the bench to bedside and from economic evaluations.

(Top 5) To promote education for appropriate job qualifications and better social integration
Due to its multi-disciplinary and interdisciplinary setting, TRAIL aims at proposing new topics and a new organization of teaching, whether in the academic setting (licence, master, doctorate) or in continuing education. This will offer to students new job opportunities with perspective of doing research or in joining the commercial side of medical industries devoted to imaging.

(Top 6) To set up a strong governing organization and an internal management
According to the new policies of Bordeaux University (see section 5.2.4 Basic of governance of TRAIL).

Solutions by the LabEx TRAIL

Our project is to promote a strong organization that foster translational research in bio-imaging.

First, we need a common dynamic governing organization and an animation. About 25% of the budget will be dedicated to the structure itself over the first 5 years (2011-2015) a period at the end of which the partners will be evaluated by AERES, the French agency for Research and Education evaluation. The governing funds will be evaluated through three main indicators reflecting the quality of the coordination:

- the development of interdisciplinary partnerships in the LabEx between teams,
- the creation of a "Federation of Research CNRS – INSERM – CEA - University of Bordeaux - University Hospital - Cancer Hospital" between the partners,
- the attractiveness of new teams as LabEx partners.

Second, we need to boost our researches. High level imaging researches should have an impact on the attraction of the Bordeaux site, but is not limited to imaging researchers. Attractiveness should also concern other basic sciences (ex: biologists, chemists, molecular biologists) that would like to use high quality imaging to apply *in vivo* their own high level research developments. Calls for research projects are the core of the structuring tools of the LabEx. They represent the main bulk of the LabEx research funding envelop. Each of them will therefore be focused on one or more themes among strategic priorities of the LabEx work packages. For an example, two work packages (WP3 Dynamic Nuclear Polarization and WP6 Mathematical Simulation) are emergent and risk taking. We agree already to prioritize the first call (2011) for these projects. The five other WP, are more advanced however they need to be boosted for increasing cooperation among different teams and disciplines, and for the translational process in order to be applied to humans. Several calls for research projects will encourage research projects jointly supported by several teams of LabEx and also cooperation with research teams from other (international) universities. In addition, the evaluation will prioritize projects that will search at finding solutions for T1 and T2 translation.

Third, the LabEx will foster the setting up of the International Bio-Imaging Master of Bordeaux, starting September 2011, exclusively taught in English in order to be internationally attractive and to prepare students to mobility, reading and working in English. Several of the teacher-researchers (professors, associate professors) of the IBIO Institute and the LabEx project participate to the master teaching in addition to their participation to several other master courses and teaching at the medical school. Based on annual calls for mentoring programs and interdisciplinary animation (such as developing skills for writing papers, teaching, publication strategy, setting up interdisciplinary seminars and workshops with international guests speakers, …) we will offer a broad and diversified range of learning activities. Another very important group is the PhD students. **We wish to develop PhD student stipends through an annual call.** This action will allow our own selection of PhD students that will include a pre-selection of the projects submitted and an oral examination of the pre-selected candidates. Finally, we will encourage the participation of the private sector (industries, CRO, associations of patients, …) to teach in Masters or PhD degrees, to offer internships and to support financially the calls organized by the LabEx. Solutions of funding through the Foundation of Bordeaux University (a support structure of the LabEx) are offered to industries. Recently we obtained a 350.000 euros private funds from a radiological association for education in the field of Bio-Imaging. Our IBIO Institute and LabEx project has also raised funds with a recent engagement of AGFA company (see letter in annexes) with an initial investment of 240.000 euros dedicated to promote education and research.

Fourth, we need businessmen from medical industries (devices, contrast agent, pharmaceutical companies, …) to better understand the potential of development of our researches and teaching activities, and in the other hand we wish to alleviate researchers from administrative or commercial approaches. To organize the mutual understanding, we want to offer a one-stop industries service for the entire IBIO Institute and LabEx project, with respect of general rules for patents, transfer and valorisation in close coordination with the SATT of Bordeaux and other professional offices. We need to recruit a business developer (2011-2012) that will organize the one-stop service, will directly canvass industries and business offices, will display to the industries and private sector a good understanding of our researches and teaching activities. The initial salaries will come from LabEx funds to secure a non-tenure position for four years. After four years, in case of success, private funds should take over LabEx funds.

➨ **SCIENTIFIC PROGRAMME IN DETAILS**

From bench …

WP1: MRI GUIDED HIGH INTENSITY FOCUSED ULTRA-SOUNDS

MRI guided High Intensity Focused Ultrasound (MRI guided HIFU), is a new technology that appears destined to play a significant role in future healthcare.

Short summary : The possibility of locally heating tissue without doing harm to surrounding tissue opens a pathway towards new therapeutic strategies with improved liability and less associated trauma, leading to improved efficacy, reduced periods of hospitalization, reduced treatment costs and improved quality of life [14, 15]. Our objectives are on one hand to treat tumours in different organs with MRI guided High Intensity Focused Ultrasound, on the other hand to develop the concepts of local drug delivery and local control of gene expression.

To further develop MRI guided High Intensity Focused Ultrasound towards treatment of tumors in particular for liver and kidney, as well as breast and prostate from large animals to clinical trials.

Objectives : 1) The development of MRI guided HIFU for thermo-ablation of cancer in liver and kidney, as well as breast, and prostate from large animals to clinical trials;

2) The development of MRI guided HIFU for image guided drug delivery to achieve a) local release of drugs from circulating nanocarriers, b) extravasation of drugs, c) crossing natural barriers such as cell membranes, blood-brain-barrier [25, 26].
Theme 1 is clearly translational in character. Some aspects in theme 2 will have a clinical component, in particular when using existing nanocarriers and ultrasound contrast agents. For entirely new nanocarriers, the timeframe may be too short to reach the clinic.

Developments in LabEx : Task 1: 2010-20 - New procedure for tissue ablation based on local heat

- New methods for volumetric heating under MRI control, motion correction, target tracking, and intercostal firing (8 patents since 2000)
- Potential alternative for radiotherapy with conceptual similarities but with the following advantages :
  - Real time image guidance, motion correction, and therapy assessment
  - No apparent cumulative dose for nearby healthy tissue (so long as thermal dose is controlled)
  - Noninvasive, rapid procedure with short hospitalization
  - Need for multi-site clinical trials to prove the validity of the concept in the cancer field

Task 2: 2010-20
The concept of local drug delivery uses MRgHIFU with heat-sensitive nanocarriers and drugs is another challenge to increase drug efficacy while reducing toxicity. We are part of the
European Consortium “Sonodrugs”, focusing on methods for controlling doxorubicin release
within liver tumors with thermosensitive nanovehicles.

Task 3: 2010-20
In Gene and Cell Therapy: local control of gene expression
The combination of MRI-guided HIFU heating and transgenes under control of heat-inducible HSP (Heat Shock Protein 70) promoter provides a direct, noninvasive, spatial control of gene expression via local hyperthermia.

Attractivity

We are among world leaders in that field. This position guarantees a strong attractivity for high-level scientific collaborations.

Collaborations and Valorizations:

Creation of a start-up company (IGT, 2002) and a technology transfer unit (Yasmina Berber, 2009)
Collaboration with Philips Healthcare at the highest level
Collaborations with several other companies (Celsion, Imasonic, SonoDrugs partners)

WP2: MRI NEW CONTRASTS AND NEW SEQUENCES

General objectives:

To increase spatial and temporal resolutions, increase sensitivity, increase specificity to become more quantitative and to adapt NMR/MRI to systems biology.
The effort will be focused on the development on 3D, real-time and whole body sequences for morphological, functional and molecular and cellular MRI [27, 28].
The project will be divided on three main and interconnected steps: sequences design and implantation, preclinical evaluation on small animals and transfer to clinical research and applications.

Task 1. New sequences for anatomical imaging

The main objective is to develop real time 3D TrueFISP sequences for brain and whole body explorations. The strong point of these sequences is to generate images, with high contrast, high signal-to-noise ratio with a very high spatial resolution. The main challenges of this research task is the implantation of this sequence at high and very high field for preclinical and clinical imaging (7T and beyond). The final goal of theses sequences is to better evaluate and quantify tumor volumetry and to detect and map cancer metastasis in a non-invasive manner. After the preclinical evaluation and validation, the concept will be proposed to MRI manufacturer to facilitate the transfer to clinical research.

Task 2. New sequences for functional imaging

In the field of macro-vascular exploration of the mouse (angiography and flow quantification), an unique flow quantification method has been developed by UMR 5536 and validated on many pathological models.
After optimization of the proposed flow quantification methods, the concept will be proposed to MRI manufacturer to facilitate the transfer to clinical research. The method has a high potential in term of early diagnosis of cardio-vascular pathologies.

Task 3. New sequences for molecular and cellular imaging

The aim of molecular and cellular imaging is to contribute to the development of new diagnostic and therapeutic strategies. Targeting agents are biological molecules or biocompatible nano-objects used as smart contrast agents for revealing a specific biological activity. The main effort will be to develop very original tools for whole body imaging sequences in order to detect and follow the new contrast agent inside the animal and further in the patient. The biodistribution evaluation of multi-modal nanoparticles associating multi-modal contrast agent and drugs is one of the main goal of this task.

Collaborations

For the three proposed tasks, project teams will be built with experts of the domain inside and outside the labex, in order to collect the complementary expertise.

WP3. DYNAMIC NUCLEAR POLARIZATION

New Targeted DNP-Contrast Enhanced MRI for diagnosis through protease spotting and use of dynamic nuclear polarization and specific free-radical-based contrast agent to target disease-associated protease activities

Magnetic resonance detection and quantitation of highly diluted species is a challenge, especially in vivo. A way to increase the visibility of molecules of interest is to use Dynamic Nuclear Polarization (DNP) that in principle allows huge increases in Magnetic resonance signal. DNP can be performed by magnetization transfer from the free electrons of a stable radical substance towards either the hydrogen atoms of surrounding water molecules classically observed by Magnetic Resonance Imaging (MRI) or the 13C nucleus of tracer molecules. There are very few teams having an expertise in dynamic nuclear polarization (DNP) for in vivo applications: 6 in the United States and 6 in Europe (including one in Bordeaux). Bordeaux is the only centre where both DNP by electron-proton Overhauser effect (in vivo DNP) for enhanced MRI and DNP of 13C metabolic tracers (dissolution DNP) will be used [29]. The second leg of this workpackage concerned the implementation of the first dissolution DNP center in France. This facility will represent a unique metabolic imaging tool for scientists and MDs in oncology, neurology, cardiology and pneumology laboratories from the Bordeaux area. This project is part of an European initiative for promoting and developing molecular and metabolic applications of in vivo MRI. Strong attractivity towards industry is expected in the field of drugs, contrast agent and MR devices.

WP. 1 In vivo DNP to target Task.1 Design of FDA-approved nitroxides for protease targeting (2011-2020diseases associated protease activities

New Targeted DNP-Contrast Enhanced MRI for diagnosis through protease spotting and use of dynamic nuclear polarization and specific free-radical-based contrast agent to target disease-associated protease activities

Laboratory-scale design of DNP-compatible nitroxydes with protease signature 2011-2014; Collaboration UMR 6517, Marseille; Toxicity assay 2013-2015; Scaling-up, Patenting and Licensing / FDA approval process 2015-2020 Company to be found

Task2 Feasibility and pre-clinical tests of DNP-MRI at constant field

Feasibility of in vivo DNP in MRI system at low field: animal study 2011-2013; In vivo protease spotting by DNP-MRI in animal models 2012-2014

Task3 Building-up of new equipment

Design and manufacturing of a field-cycled MRI system for DNP-MRI in small animals 2011-2013 MRI manufacturer to be found; Design and manufacturing of a field-cycled MRI system for DNP-MRI in large animals and humans 2013-2015 MRI manufacturer to be found

Task4 Preclinical evaluation of the new equipment

Feasibility of in vivo DNP in the field-cycled MRI system at low field: in vitro and small animal study 2012-2014

Feasibility of in vivo DNP in the field-cycled MRI system at low field: large animal study 2014-2016

Task5 Preclinical evaluation of protease spotting in vivo with field-cycled DNP-MRI

In vivo protease spotting in field-cycled MRI system at low field: in vitro and small animal study 2016-2018

In vivo protease spotting in field-cycled MRI system at low field: large animal study 2018-2020

Task6 Clinical trials: Equipment installation in Bordeaux Hospital

From 2020 - Costs to be defined at that time

WP 2. Dissolution DNP for high sensitivity metabolic and molecular MR in vivo imaging

A very efficient approach to overcome the low sensitivity of MRI or MRS techniques is based on nuclear hyperpolarization and the subsequent creation of giant macroscopic nuclear magnetization located on molecules of interest. Dynamic nuclear polarization (DNP) techniques applied to (C13, N15...)-labelled biomolecules path the way to in vivo metabolic and molecular pre-clinical and clinical applications of MR imaging. The first endpoint is the implementation of dissolution DNP facilities available to the scientific and medical community of the Labex core laboratories. The second endpoint is the approval of dissolution DNP device for clinical studies.

Task1 Feasibility of in vivo dissolution DNP in animal studies, 2011-2013.

Task2 Investigation of animal model of disease. 2013-2020.

Task3 Validation and certification procedure of the device for clinical investigation, 2015-2020.

This WP will interact back and forth with WPs 2,4 and 5 (MR sequences, contrast agents and biomakers). Main outputs of the WP concern the applications of excellence in oncology, neuro, cardio and pneumo. International collaborations are established in the framework of a european initiative gathering academic groups in Cambridge, EPFL, Torino, etc. and industrial partners (Bracco spa,…)

WP4. TRACERS AND CONTRAST AGENTS

Our research will be developed in the field of labelling selected ligands (i.e. peptides and aptamers, see biological markers) by different methods involving either covalent or coordination labelling methodologies.

1. Carbone 11 and Fluor 18 labeling, for PET imaging.

Since organic chemistry is based on carbon chemistry, the incorporation of ^{11}C in biomolecules benefits from the unique richness of ^{11}C-C bond formations in terms of variety, efficiency and rapidity [30]. As a consequence, the use of ^{11}C for any research project appears unquestionable and fully complementary to the ^{18}F approach. In this context our group has already developed new methodologies for the ^{11}C labelling [31] of small targets to be used for neuroimagery.

In parallel we also turn our attention to oligonucleotides and peptides, for which this chemistry becomes even more challenging. In this context, we developed an efficient one-step no carrier-added nucleophilic ^{18}F-fluorination of oligonucleotides under mild conditions [32], by modifying a thymidine and using silicon-fluorine based chemistry described by Ametamey [33]. This modified thymidine was incorporated into a model sequence of nucleotides (5'-d(GACTGACGC)-3') and was then successfully fluorinated. These promising results now open the way for radiolabeling new aptamers or modified peptides developed in this project.

2. Gallium 68 / Gadolinium incorporation, for multimodal imaging.

Among the various imaging modalities currently available, the radionuclide technique offers the highest sensitivity, but radiation limits the possibility of longitudinal studies. However, the tracer component a metal ion (Ga-68) chelated with multifunctional macrocyclic agents exhibited comparable coordination chemistry than gadolinium (Gd). Thus, we intend to work in the field of designing and synthesis of probes simultaneously capable of being used in more than one imaging modality like PET and MRI and we have developed Ga/Gd based probes of these 'designer switchable' radiopharmaceuticlas / magnetopharmaceuticals, by incorporating Ga or Gd complex of N4O3(N- or C-functionalized) system, which will be meeting the requirements for a potential imaging agent.

Objectives: To create responsive agents for molecular imaging, using different imaging modalities towards functional imaging (MR, PET and Optical)

Tasks and Schedule:

WP4.1- Design of covalent and coordinative labelling strategies

(2010-14) Innovative strategies for labelling with C11 and F18
(2011-16) Application to the labelling of nucleosides, oligonucleotides, peptides and analogs
(2012-16) Feedback from preclinic to chemical optimization
(2010-14) Labelling with coordinated Ga68 and application to selected peptides

WP4.2- Multimodal Imagery

2010-11: Design of adaptable templates; 2010-12: Application to Ga68 / Gadolinium bimodal approach;
2010-12: Application to Gd / F19 bimodal approach; 2014-17: Application to F18 / Optical bimodal Imagery

WP4.3- Preclinical trials (with labex teams)

2011-13: Selected peptides labelled with *F18*; 2011-14: Selected aptamers labelled with *F18*
2011-13: Selected peptides labelled with *Ga68 / Gd;* 2014-18: Preclinic studies with *Gd / F19* bimodal probes

WP4.4- Clinical Research (with labex teams)

2012-18: Diagnosis; 2012-18: Selection of responders for targeted therapy; 2012-18: Follow up of therapeutic response

International Collaborative Network:

Consortium including London(UK), Hannover (GE), Barcelona (SP) and Uppsala (SW)

Potential users :

1- Academics (INSERM, CNRS, Universities, and Hospitals)
2- Industrials *(Guerbet, GE-healthcare and IBA)*
3- International IP

WP5. BIO-MARKERS FOR BIO-IMAGING

Principles

Creating non-invasive interactive tools as imaging biomarkers by defining the spatio-temporal resolution of molecular and cellular events in response to pathophysiological modulations in defined diseases, with particular focus on processes involving tissue inflammation and immune modulation. The developed imaging biomarkers will serve in prediction of patients at risk, in diagnosis of patients, in evaluation of disease progression, in disease prognosis and in evaluation of therapeutic interventions [3].

Introduction

The generated pathophysiological processes of altered homeostasis, immune modulation, cellular migration and proliferation, with protein synthesis and tissue formation and remodelling involve the infiltration of immune competent cells among which monocytes/macrophages present remarkable plasticity, the degradation and remodelling of the extracellular matrix by proteases, particularly matrix metalloproteases (MMP) and the synthesis of growth factors (like VGEF, PDGF) for promotion of tissue repair and cell proliferation [34]. As many of these pathophysiological modulations are occurring at the endothelial or epithelial barriers they provide potential advantages of accessibility for molecules. Linked to imaging agents such biomarkers have the application potential for in vivo imaging, diagnosis and drug vectorization.

Objectives

To define biomarkers of pathophysiological events we have elaborated two major strategies:
1) The tropism of cellular infiltration (macrophages, T cells, mesenchymal stem cells) into the affected organ suffering of inflammation. Tracking of these cells in inflammation of multiple organs (kidney, CNS, lung) and cerebral tumours is performed upon in vivo or ex vivo labelling with iron oxide containing contrast agents upon i.v. administration [35-39]. Further developments will exploit the labelled cells (mainly macrophages and stem cells) for therapeutic approaches and as drug carriers.
2) Three chemical families of ligands based on combinatorial processes were developed:

a) *Aptamers*, i.e. structured DNA, RNA or oligonucleotides are selected from a randomly synthesized oligonucleotide library after iterative rounds of selection / amplification according to a process named SELEX (Systematic Evolution of Ligands by Exponential) enrichment. When conjugated to different chemical groups aptamers retain their initial binding properties and can be further modified for in vivo imaging (MRI, PET) by incorporation of radioelement tracers (Gd, F, C) [39].

b) *Recombinant monoclonal human antibodies* are selected from a randomly expressing phage library upon in vivo administration to define vascular alterations. The team of G. Clofent-Sanchez has the internationally recognized exclusive expertise in rapidly obtaining human monoclonal antibodies (Mabs) or their fragments (scFv, Fab'2) to detect in experimental atherosclerosis cellular and molecular targets that are over-expressed on the vulnerable atheroma plaques [40].

c) *Targeting peptides obtained by in vivo phage display selection* explores the full complexity of combinatorial DNA libraries expressing short peptide sequences without “a priori” hypotheses of the molecular target [41,42]. The team of K. Petry has developed a subtractive DNA hybridization technique adapted to short DNA sequences representing different repertoires [43]. Administration of the identified peptide ligands at defined (potentially early) stages of lesion formation could have an inhibitory effect by competing with the target on immune cell adhesion / binding and CNS infiltration. Peptide ligands mediated drug vectorization under the control of MRI will be further developed.

Schedule

Molecular Makers
Ongoing – 2015: In vitro approach – predefined targets Aptamers (MMPs) and In vivo approaches: Recombinant antibodies (Artherosclerosis); Recombinant Peptide ligands (Neuroinflammation); Comparison of Repertoires (Disease – Healthy)
Robotising of screening processes
Ongoing: Aptamers (CTT – SELEX platform)
2011 – 14: Peptide Ligands (CTT PTIB platform)
Automatisation of bioinformatic data assembly of identified proteins

2013-2015 Cellular Expression profiles (GEO); Function identification (Gene-Ontology); Interaction (Interactome); Cell signalling and Metabolism (KEGG)

Preclinical evaluation of biomarkers (diagnosis / drug delivery)

Ongoing – 2015 MRI contrast agents; Radiotracers; Nano-cargos for drug delivery / release

Clinical evaluation of biomarkers

2016 – 2018: Neuro-Oncology / Drug delivery

2018 -2020: Neurodegenerative / inflammatory diseases (Diagnosis / Patient evaluation)

Ongoing – 2015: In vivo approaches / predefined cell tracking with nanoparticles / cell specific tracers

WP6. Mathematical Simulation and Modeling

Introduction

Modeling consists in establishing a mathematical description of a system. Physiological modelling aims at integrating the key biological and physical features of a system as quantitative metrics related by mathematical operators. The resulting computer models are both descriptive and predictive, meaning that following a given parameter change (input), simulation output predicts what could occur in the real world. A growing number of medical applications have recently emerged, along with the constitution of international research networks in the field (Virtual Physiological Human and Physiome projects) [44,45]. Computer modelling can be used to understand the pathophysiology of diseases (for example extracting a parameter that cannot be experimentally measured), to predict the spontaneous outcome of diseases, or to compare treatment strategies.

The development of patient-specific modelling strategies might become feasible in the near future to enhance diagnostic performance and individually tailor therapy.

To this day, the integration of modelling strategies in clinical decision making is yet to be achieved. In each field of application, this should require a first step of methodological research (accurate co-registration between imaging modalities, accurate parameter extraction from images, model customization adapted to the given prediction task), and a second step of clinical research (mutual validation between imaging and models, impact on clinical decision making and patient outcome, cost-effectiveness).

The scientific project of the LaBEX TRAIL in computer modelling will focus on 2 fields: oncology and cardiac electrophysiology.

Oncology

The aim of this project is to propose a comprehensive study of the modeling of tumor growth, including microscopic (cell level) and macroscopic (tissues and organ level) elements and to apply these modeling tools to therapeutic innovation in oncology [46]. The long-term goal is to improve drug delivery protocols for clinical trial. We are developing a generic and complex model of cancer growth, with a modular structure, which gathers various phenomena (cell cycle, apoptosis, mechanical aspects, angiogenesis, influence of treatment : chemotherapy, radiotherapy). This global model has already been tested in various cases, parameterized in a careful way and has been used for various applications [47]. It gives us a substantial advantage with respect to the other teams that are working on cancer, and which often concentrate on only one aspect [48]. The aim of this project is to push forward this advantage by studying optimization and control issues on this model.

Actual state: At the moment we have developed a novel technique that relies on parameter estimation using temporal series of MRI or scans and applied it to the prognosis of lung metastasis from different origin.

Project: We want to develop image-driven simulations that will be patient-dependent and that will allow to predict the evolution of the disease with or without treatment. This could lead to a software used for helping the prognosis of the disease and to adjust the time of treatment. The final goal is to create user-friendly software tools that can be used in a clinical practice.

The project is divided in 4 steps:

Task 1 2011-14:Modeling of tumor growth with data given by morphologic and functional imaging (: angiogenesis, diffusion of water molecules, tissue elasticity, tumoral oxygenation).

Task 2 2014-20: Modeling of tumor growth including response to drugs

Task 3 : 2013-17: design of a software for lung tumor growth prediction ,

Task 4 : 2016-20 : application of the software model for other tumors (brain, liver)

Prospective: In the first road block "T1": In clinical and pre-clinical studies these tools may help the clinical research and the industry to validate the use of new drugs. This project may impact the second

roadblock "T2" in daily oncologic decision practice. The prediction and a better knowledge of the tumoral growth may improve the treatment planning.
Means: The LabEx will create a structured framework for research activities that demand an interdisciplinary team of investigators with a well established setting for collaboration and exchange, with expected benefits from the relationship with other WP (WP2, WP4). In particular this proposal is complementary to that presented on Numerical Certification by the University of Bordeaux, where the mathematical investigation of tumor growth models represents one of the research directions. Moreover this LabEx will provide us with the resources for appropriate technical support in terms auxiliary personnel for image acquisition and processing.

Cardiac electrophysiology

Research on cardiac modeling will focus on 2 diseases: ventricular arrhythmias and heart failure. The objectives will be to better understand the substrate of diseases, to predict their spontaneous outcome and to improve treatment efficiency (cardiac ablation in ventricular arrhythmias, bi-ventricular pacing in heart failure). Myocardial scar and myocardial mechanics will be assessed with MRI on large animals in vivo, and diffusion tensor imaging will be performed on explanted hearts. These MRI data on myocardial scar, mechanics and fibrillar architecture will be correlated to histology, conventional electrophysiological mapping, and optical mapping.
In patients, the 3T MRI will enable us to perform a 3D imaging of scar at high resolution, as well as a 2D quantitative T1 and T2 mapping of the tissue. Myocardial strains will be assessed with the use of DENSE MRI at high temporal resolution. The output will be 3D meshes of the myocardium displaying scar intensity or myocardial strains as scalar data. These models will be integrated in the electrophysiological navigation platforms.
In patients suffering from cardiac arrhythmias, MRI derived models will be used as the basic geometry on which endocardial or epicardial electrical mapping data will be mapped at high resolution. This will result in an accurate co-registration of quantitative electrical and tissular data.
In heart failure patients, these models will be used for navigation purposes during pacing procedures in order to co-register data at the pacing site (position on the model, acute response to pacing).
Besides this navigation use, the patient-specific cardiac models derived from MRI will be submitted to computer simulations in order to reproduce diseases in silico, and to compare various treatment strategies (number and position of pacing sites in heart failure, ablation targets in cardiac arrhythmias). Results of these simulations will be validated on experimental data acquired in patients during pacing and ablation procedures.

The tasks of our research on cardiac modeling will be organized as follows:
T2.1 2011-2014: Navigation on image-based cardiac models during pacing and ablation procedures
T2.2 2011-2014: Computer simulation to predict outcome after bi-ventricular pacing in heart failure
T2.3 2011-2014: Computer simulation to predict outcome after ablation in ventricular arrhythmias
T2.4 2014-2020: Impact of cardiac modeling applications (navigation/simulation) on clinical decision making

This research will be performed in collaboration with the INRIA Asclepios team (INRIA Sofia Antipolis), within the IHU LIRYC and EQUIPEX EP-XMR consortiums. It will benefit from the support of the LaBEX TRAIL teams dedicated to MR methodology (WP1, WP2) and Cardiac imaging (AE3). Within the LaBEX TRAIL, research will aim at improving acquisition methods (MR methodology), data extraction (image post processing), and inter-modality fusion (co-registration).

The valorization of this research should be substantial. The ability to predict the occurrence of ventricular arrhythmias based on scar morphology should lead to a better prevention of sudden cardiac death, resulting in major savings for the patients and the community. Beyond this medico-economic impact, new treatment strategies will certainly emerge from computer simulations, which should lead to the development of new devices (ablation devices, pacemakers...). Besides, the ability to perform virtual electrophysiological procedures on training simulators might help to spread these newly developed therapeutic approaches in the cardiology community.

WP7. STRUCTURAL/FUNCTIONAL NEUROIMAGING TOOLS FOR PRECLINICAL, CLINICAL AND POPULATION STUDIES

Introduction

Although 3T is likely to stay for several years the optimized magnetic field strength for many clinical research protocols, it is now recognized that ultra high field magnets (>7T), because they give access to increased MR signals, will be mandatory to perform advanced integrative neuroscience, and maybe in the future necessary for understanding human brain function, advanced diagnosis of degenerative and/or inflammatory neuropathologies. Accordingly, it is expected that the Bordeaux site will have in the near future several high field (HF) MRI for preclinical and clinical neuroscience research. This HF-MRI platform will require methodological development and updates on both the data acquisition and the data processing sides. Whereas WP2 will deal with development in data acquisition, it is the goal of WP7 to develop, implement, maintain and update a platform of dedicated tools for the implementation structural and functional neuroimaging.

Workplan

Task 1. A complete set of MRI sequences for cognitive neuroimaging, especially that developed in WP2, will be implemented and validated, both at 3T and 7T when available. Such sequences concern both structural (T1, T2, FLAIR and DTI) and functional mapping (BOLD, EPISTAR) in humans and non-human primates.

Task 2. Complete sets of MRI compatible devices necessary for functional imaging experiments will also be implemented on 3T/7T machines, including those for 1) delivering and recording the response to somatosensory, visual, and auditory stimuli, 2) recording eye movement, 3) monitoring physiological parameters. Computerized psychometric batteries

Task 3. Unsupervised automated pipelines for an up-to-date analysis of structural/functional brain image series will be implemented. Such pipelines are mandatory for large cohorts of subjects, a domain in which the Bordeaux teams have an undisputed leadership.

Task 4. Building upon an on-going ANR project, the Bordeaux node will also develop the environment for non-human primate MRI studies (macaques), as TRAIL intends to host such translational protocols.

Past experiences and collaborations

The “Groupe d’Imagerie Neurofonctionnelle (GIN, UMR6232)” staff has developed image automated processing pipelines, including dedicated imaging tools (AAL, WHALE), and database structure and management systems that will serve as starting points for the above described WP7 tasks. In addition, being affiliated with the International Consortium for Brain Mapping (ICBM), TRAIL will have access to the numerous methodological developments made by ICBM members. These works will also benefit from a close collaboration with the 7T manufacturer and the installation of a second generation of more technically advanced 7T MR systems.

… To bedside: imaging researches applied to clinical medical sciences

A1. ONCOLOGY

Introduction

This programme has two aspects: on the one hand the diagnostic aspect, oriented towards molecular imaging, allowing an integrative approach to tumours from a functional, metabolic and molecular point of view and not just a morphological one. On the other, the treatment aspect, oriented towards interventional imaging with thermotherapy and the development of novel therapeutic strategies such as targeted local delivery of drugs.

Molecular and functional imaging, as well as mathematical models, play now a major role for characterization of tumor phenotypes, for understanding the complexity, diversity and *in vivo* behaviour of cancers, taking into account the specificity of tumor microenvironement (as angiogenesis, pO_2, cell density and proliferation, apoptosis…), for a better adjustment of targeted therapies.

Objectives

1. In the field of nuclear medicine we developed a dual research expertise: 1) in synthesis of new radiopharmaceuticals, as aptamers and peptides, with new methods of radiolabeling the later with Gallium 68; this is developed through an international consortium directed by GE Healthcare, which could be enhanced by a new project of mini-cyclotron through the Equipex call. We have synthesized two molecules, the [18F]-FMISO (hypoxia tracer cell) and [18F]-FLT (tracer of proliferation) that are currently being validated in 3 clinical research protocols. 2) To develop methods for quantifying signal taking into account the partial volume effects and respiratory motion for a better tumor delineation.
2. In collaboration with the CEA-LETI and the Vermont US company (Tours), we developed an original and unique system of bi-functional, optical-US, system for detection of prostate cancer (ANR 07) allowing, using targeted optical probes (collaboration with the Fluoptics company) to detect and biopsy specifically prostatic cancer. The next steps will be : 1) to end-up with endorectal prototypes to be tested on tumor models in small, then big, animals before first clinical testing; 2) to develop an optoacoustic imaging prototype being able to reach deep prostatic tissues.
3. Mathematical models (see WP6) may be applied to tumoral growth for a better adjustment of treatment in terms of timing of delivery. These models have been applied to lung tumors after extraction of tumoral volume. Our aim is to propose a comprehensive modeling of tumor growth, including microscopic (cell level) macroscopic (tissues and organ level) elements (in silico modeling) and to integrate functional parameters provided by imaging such as angiogenesis, diffusion of water molecules, tissue elasticity and oxygenation.
4. In the therapeutic field, we have developed two original image-guided approaches:

- MRI-guided focused US for noninvasive tumor ablation with online data processing. We are also among world leaders in that field.
- Local drug delivery is another challenge to increase drug efficacy. We are part of the European Consortium “Sonodrugs”, focusing on methods for controlling doxorubicin release within liver tumors with thermosensitive nanovehicles. The theme is also supported by the Foundation InNaBioSanté.

Collaborations outside IBIO

National : INSERM U 563, Toulouse (F Courbon) : TEP ; INSERM U 650, Brest (D Visvikis) : TEP; CEA-LETI, Grenoble (J Boutet) : FMT and Optical-US probe; MC2-INRIA, Bordeaux 1(T Colin) : Mathematical models

International : INMAS, New Dehli (A Mishra) : TEP; **National Cancer Institute, NIH, USA:** Image guided Drug Delivery; Partners of the SonoDrugs Integrated project (www.sonodrugs.eu): Image guided Drug Delivery

Industrial : General Electric (USA) : TEP; Philips Medical Systems (NL) : MR-guided FUS; Imasonic (F) : US transducers for FUS; Vermont (F) : Optical-US probe; Fluoptics (F): Optical tracers; Guerbet Group (F) : Contrast agents; Industrial partners of the SonoDrugs Integrated project (www.sonodrugs.eu): Image guided Drug Delivery

A2. NEUROLOGY

Past activities of Bordeaux neuroimaging teams

Over the past years, the three Bordeaux neuroimaging teams have conducted research in two main topics, namely: 1- the structural and functional brain underpinnings of cognition in normal adults and their evolution during aging, 2- the study of white matter lesions in aging as well as in neuropathologies such as multiple sclerosis (MS), cerebrovascular diseases and dementia. In these few but very specific topics, the Bordeaux team research is widely recognized and for some they share international leadership.

Neuroimaging research objectives in the TRAIL

Objective 1: Neuroimaging of degenerative and inflammation disorders: pathophysiology, diagnostic and therapeutic tools

The project will amplify ongoing studies on the physiopathology of MS/experimental models to develop in vivo markers of neuroinflammation events and new therapeutic strategies under the control of MRI and PET (see WP2, WP4, WP5 and WP7).

Task 1: Characterization of the ambivalent macrophage activity in inflammation and repair;

Task 2: Defining spatiotemporal events of molecular alterations in BBB opening;

Task 3: Screening and generating peptide ligands as targeting molecules for drug delivery;

Task 4: Understanding the basis of cognitive reserve capacities and the activation of cerebral neuronal networks in MS patients by applying functional MRI analysis. A somewhat similar strategy will be implemented regarding AD for which tissue damage in demented patients will be explored using texture-MRI analysis and PET molecular imaging. We will focus in particular on the role of hypoxia, a direct consequence of hypo perfusion, and inflammation associated to the repair of vascular damages related to vascular risk factors.

Objective 2: Cognitive neuroanatomy in cohorts of normal adults and pathological aging: risk factors and biomarkers

In collaboration with the Bordeaux INSERM centre for epidemiology, we have the ambition to establish Bordeaux as one of the world leading places in neuroepidemiological imaging. The project will be based on several cohorts, either already established or to be started, and will be based on a common reference framework combining state-of-the art neuroimaging equipment and image processing tools (see WP2 and WP7), standardized psychometric batteries, and DNA sampling. In normal adults, a first goal will be to identify factors and biomarkers of human brain structural and functional variability, a project ignited with the 300 subjects BIL&GIN cohort. With i-Share, an entirely new, prospective cohort of 30,000 students followed for at least 10 years, it is proposed to perform MRIs in 3,000 of these students, including 1,000 randomly selected participants. A third category of protocols will concern prospective cohort studies and controlled clinical trials in elderly subjects. In particular, using additional imaging techniques and novel methods of ambulatory monitoring, we will open a wide field of research options where it will possible to characterize disease-specific brain changes, identify individual risk factors or markers of vulnerability, thereby enabling ecologically-valid, repetitive, non-invasive disease staging and measurement of therapeutic outcomes.

A3. CARDIOLOGY

Introduction

Heart diseases are the first causes of mortality in Human being in the world. The scientific project of the LaBEX TRAIL in cardiology will focus on 2 main themes: myocardial ischemia and cardiac electrophysiology. Part of research will be dedicated to methodological developments in imaging, image processing, modeling and simulation, the other part being devoted to clinical research on the realm of cardiac disorders included in our field of expertise: coronary artery disease, heart failure, atrial and ventricular arrhythmias. The objectives of our research are three-fold: (i) to understand the pathophysiology of diseases, (ii) to detect, monitor and predict the outcome of diseases, and (iii) to guide therapeutic procedures.

Endpoints

Ischemic cardiomyopathy

It is established that morphological criteria on angiography are not sufficient to evaluate the functional impact of coronary stenoses, and to guide invasive treatment procedures [49]. Because cardiac magnetic resonance (CMR) under adenosine or dobutamine stress can quantify coronary and contractile reserve at high spatial resolution without radiation exposure, while at the same time assessing myocardial viability, it can be considered as a promising tool for detection, characterization, and monitoring of coronary artery disease [50]. On the other hand, non invasive methods indirectly assessing coronary function through a study of myocardium may be limited for disease characterization, because the analysis is performed on a vascular territory, whereas the target of invasive treatments is the stenosis. To date the access to coronary function on the stenosis scale is only possible with the use of invasive methods (guide wire with pressure and/or velocity sensors), which were proved useful for therapeutic decision making [51]. In collaboration with the CNRS UMR5536 team, we have demonstrated the feasibility of a 3D assessment of coronary velocities in small animals with the use of MRI [52].

The specific tasks of our research in ischemic cardiomyopathy will be:

T1.1 CMR stress imaging for the clinical management of coronary artery disease

2012-2016: Clinical validation for the detection and characterization of coronary stenoses

2014-2020: Impact on clinical decision making in coronary artery disease

T1.2 3D coronary velocity mapping: translation from small animals to humans

2012-2013: Transfer of pulse sequence on clinical scanner

2013-2014: Assessment of feasibility on phantoms and human volunteers

2014-2016: Validation versus invasive velocity measurements

2016-2020: Impact on clinical decision making in coronary artery disease

Cardiac electrical disorders

Cardiac resynchronization therapy (CRT) with bi-ventricular pacing has recently emerged as an alternative to heart transplantation in patients resistant to medical therapy. However, up to 30% of the patients do not show a favorable response after implantation [53], and some data are suggesting that in responders, the benefit could be doubled by carefully selecting the left ventricular pacing site [54]. Because MRI has the unique ability to give access to intra-ventricular, inter-ventricular, and atrio-ventricular mechanical synchrony [55,56], global and regional contractile function, and myocardial viability [57], it can be considered as a promising method for the evaluation of patients prior to CRT, as well as for the study of the mechanisms involved in bi-ventricular pacing.

Cardiac arrhythmias, namely atrial fibrillation (AF), ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (SCD), have recently benefit from the development of new treatment strategies, based on the ablation of the so-called “arrhythmogenic substrate”. To date, the identification of treatment targets is based on a refined analysis of detailed electrophysiological contact mapping data. Scar imaging with the use of CMR has recently emerged as a complementary tool to assess the structural substrate of diseases, and preliminary studies suggest a potential value in the prediction of response to AF ablation [58], in the assessment of ablation completeness in AF [59], as well as in the prediction of SCD and occurrence of VT [60]. Besides this exploratory use, CMR has been proved feasible for real-time monitoring of tissue temperature during thermo-ablation in various organs [61]..

The specific tasks of our research in cardiac electrical disorders will be:

T2.1 MR thermometry in cardiac ablations

2012-2015: Feasibility study in large animal models and humans

2015-2020: Clinical validation vs standard procedures

T2.2 Structure-function correlation studies in cardiac arrhythmias

2012-2015: Impact of scar on atrial and ventricular arrhythmogenic substrate

2012-2020: Impact of fiber orientation on atrial and ventricular arrhythmogenic substrate

T2.3 Purkinje network imaging

2012-2015: Purkinje tissue targeting; 2015-2018: Development of a specific MR contrast agent

2018-2020: Feasibility studies in animal models and humans

Development in LabEX

This research will benefit from the active support of the LaBEX TRAIL teams dedicated to MR methodology (WP2), MR thermometry (WP1), Computer modeling (WP6) and Chemistry (WP4).

Attractivity

The imaging platform combining Xray electrophysiological mapping and 3T MRI technologies will be the first of that kind in France, and the only one in the world entirely dedicated to cardiac electrophysiology.
The scientific environment provided by both the LaBEX TRAIL and the LIRYC Institute will represent a world-class structure for research and teaching, attractive not only to researchers and industrial partners in cardiology, but also in radiology, magnetic resonance, image processing and computer science.

Collaborations

LaBEX TRAIL Collaborations: CNRS UMR5255 (TRAIL WP4) on task T2.4 ; CNRS UMR5536 (TRAIL WP2) on task T1.2 ; CNRS UMR5231 (TRAIL WP1) on task T2.1
The cardiology team will also participate to research on computer modelling (TRAIL WP6). Other academic and industrial collaborations will take place within the frame of the IHU LIRYC and EQUIPEX EP-XMR consortiums.

A4. PNEUMOLOGY Imaging of bronchial remodelling

Introduction

Chronic respiratory diseases (asthma and chronic obstructive pulmonary diseases (COPD)) are a major and increasing public health problem (about 6 million people are affected in France).
The general objective of this application of excellence is to understand, treat and evaluate the bronchial remodelling, hallmark of chronic respiratory diseases. In particular, one of our specific aims is to develop new non invasive imaging tools to assess bronchial remodelling *in vivo* [62]. For this purpose, this research program will combine clinical, functional, CT and MRI *in vivo* data with histological, functional, cellular, and molecular data obtained *in vitro*.

Endpoints

EP1. *In vivo* imaging (extend, grading) of bronchial remodelling in patients.
EP2. Non invasive imaging tools for evaluation of treatment efficiency in asthma and COPD.

Developments in LabEx

Task1. Lung functional imaging (ventilation, perfusion) in animal models. 2011-2014. Personal cost: 1 postdoc (60 keuros/year). Consumable: 20 keuros/year. Equipment: 100 keuros.
Task 2. Molecular and metabolic imaging of inflammatory and remodelling processes in lung. 2014-2020. Personal cost: 1 postdoc (60 keuros/year). Consumable: 20 keuros/year
Task 3. Application of intrabronchial micro-coils for MR investigation of chronic pulmonary diseases. 2012-2014. Personal cost: 1 postdoc (60 keuros/year). Equipment: 40 keuros.
Task 4. Investigation of structure-function relationship. Computer simulation of air fluxes in lungs. 2015-2017. Personal cost: 1 postdoc (60 keuros/year).
Task 5. Clinical studies in asthmatic, COPD and cystic fibrosis patients. 2012-2020.

Attractiveness

This lung imaging Application of Excellence will benefit from the integration of scientists and clinicians mastering all steps of translational research in lungs, including cellular and molecular assays, animal models, pre-clinical and clinical imaging, clinical trials and management of large patients database. This combination of comprehensive expertise, unique in Europe, will guarantee a strong attractiveness for high-level international scientific collaborations, for industry-academy partnership and for the creation of local start-ups.

Academic and Industry collaborations

This Application of Excellence will implement scientific interactions with WP2 (MR sequences), WP3 (DNP), WP4 (contrast agents), WP5 (biomarkers) and computer modelling with external academic groups. Task 1 and 5 will be implemented in the framework of a European research network (ITN Pi-Net) including world-leading groups in Heidelberg, Sheffield, etc. Industry collaborations will be pursued and reinforced with Pharma groups (Astra-Zeneca, Novartis, GSK, Boehringer).

A5. NEPHROLOGY

Introduction

Chronic kidney disease (CKD) is a worldwide health care problem with extensive morbidity, mortality and increasing health costs. Its incidence is growing due to the increase of risk factors. A better

understanding of the nature of CKD, leading to early detection and prevention and effective therapy might alleviate the global burden. Improvements have to focus on: better understanding of mechanisms leading to renal fibrosis, development of diagnostic tools to characterize these processes and development of targeted therapies. This is why we have been developing for many years imaging techniques for noninvasive characterization of renal function and renal tissue processes as inflammation and fibrosis.

Past activities

We were the first team using iron oxide particles to detect and quantify the inflammatory component of nephropathies in native and transplanted kidneys and we performed the first pilot clinical trial [37]. We were also the fist ones using techniques of cell labelling and cell tracking to monitor with MRI intrarenal cell therapies. More recently: 1) we applied techniques of in vivo control of gene expression within rat kidney using thermo-sensitive promoters; 2) we developed the techniques of elastography (shearwave US elastography and MR-elastography) to monitor intrarenal changes during the fibrotic process.

Objectives

Task 1. Functional MR imaging of renal physiology Due to the complexity of renal physiology, validation of dynamic compartment models remains mandatory to characterize the filtration function. This will be conducted in collaboration with Brighton Medical School (PS. Tofts) and the UCL Institute of Child Health (I. Gordon). This will also require the development of original post-processing image analysis as the functional segmentation of the renal compartments in collaboration with the LaBRI Laboratory. Development of new MR sequences will be also worthwhile to be able to measure R1 relaxivity dynamically, in collaboration with Partner 1 (WP2)

Task 2: Imaging of renal inflammation and degenerative renal diseases

The main objective will be to keep on developing functional and cellular imaging techniques to characterize in vivo biological processes. These objectives will require: 1) to evaluate new iron oxide particles developed by the Guerbet Group (P-904) for cell imaging and use this approach to test new drugs modulating macrophage reaction; 2) to test new agents targeting metalloproteinases (see aptamers) ; 3) to optimize techniques of MR diffusion tensor imaging to quantify the progressive changes in renal structure and anisotropy; 4) to validate the techniques of US elastography and MR-elastography for evaluation of intrarenal fibrosis.

Attractivity

Our strength is the experience we gathered in the field of functional and molecular imaging of the kidney for many years and the high level collaborations we have developed, making our group leader in France for this topic and among the 10 most involved in the world.

Collaborations in Labex: The TRAIL laboratory of excellence is an important opportunity to formalize a transverse collaborative research programme on "Imaging of Inflammation" gathering groups working in this field (WP5-WP7). Synergy between partners in term of developments of new MR sequences, new contrasts (WP2) and new targeted agents (WP2-WP4) will be highly helpful.

Collaborations outside IBIO: This programme will be conducted in UMR 5231 with essential academic and industrial collaborations, at a national or international level:

- New functional MR imaging of the kidney developed in collaboration with the MR Research Centre, Aarhus, DK (M. Pedersen), the LaBRI, U. Bordeaux 1 (P. Desbarat), the Institute of Child Health, University College, London (I. Gordon), the Brighton Medical School (PS. Tofts) and Apollo Medical Imaging Technology Pty. Ltd (Aus) for software development.
- Imaging of renal inflammation is developed in collaboration with the INSERM U567, Bordeaux 2 (C. Combe-Nephrologist, J. Ripoche-Biologist, S. Lepreux-Pathologist) and the Guerbet Group (Aulnais-sous-Bois, F).
- Renal US elastography is developed in collaboration with the CNRS UMR 7587-INSERM U979, ESPCI Paris (M. Tanter) and the company Supersonic Imagine (Aix-en-Provence).
- Renal MR-elastography is developed in collaboration with the INSERM 773, Paris (R. Sinkus) and Philips Medical Systems (Best, NL).

5.2.1.3 Epidemiology and medico-economics – the public health impact analysis of our translational T2 research

CIC-EC7 (Clinical investigation centre in clinical epidemiology 7), is an academic CTU involving four institutions as partners making it a strong link between research organisations (INSERM, Bordeaux 2 University) and hospitals (Bordeaux University Hospital, Bergonié Cancer Institute).

The CIC-EC7 covers four domains of expertise in biomedical research: epidemiology, biostatistics, medical informatics and medico-economics. All four expertises are crucial in the development of innovative imaging techniques at both the clinical and population levels.

CIC-EC7 Next 10 years program

Methodological expertise for the design of clinical studies in the field of diagnostic and for the analysis of the complex multidimensional data provided by novel imaging techniques, are scarce.
Therefore, CIC-EC7 needs to strengthen the expertise and establish strong collaborations outside the TRAIL LabEx, before entering the development of new techniques.
As soon as the new techniques developed by TRAIL Labex will be available (or planned to be available) for human studies:

- design and generate clinical development plans for the innovating imaging techniques
- collaborate with support structures in the design and implementation of clinical studies for the aspects of design, biostatistics, data management, statistical and medico-economic analysis and valorization
- develop innovative designs and statistical methods relevant to the clinical aims of the studies and the nature of data provided by the new imaging techniques.

Exploitation of results, transfer and expertise

With its programme "Investissements d'avenir", the French government makes a priority to promote projects that bring strong prospects in term of sustainable renewal and growth of the regional, national and European economy through innovation and training of highly qualified persons to operate in markets with high added value and strong growth prospects. Two very **dynamic markets in term of innovation** and knowing a continuously growth are of particular interest for TRAIL.

The medical imaging market. The world market earned revenues of US$ 5.7 billion in 2009, and is estimated to reach US$ 6.55 billion in 2012. For instance the added US and European markets for Ultrasounds systems was worth US$ 2.4 billion in 2008, expected to grow at a steady rate of 7% in the next 7 years to reach US$ 4 billion in 2015; as for the MRI global market, it was predicted to be worth nearly US$ 6 billion by 2015 thanks to a mean growth rate of 5% between 2010 and 2015. The medical imaging market is very concentrated, with 4 multinational players sharing more than two third of the world market: GE, Philips, Siemens and Toshiba. TRAIL members are already engaged in collaborations or discussions with these leading players. The development of innovative technologies also allows some SMEs to develop on niche market with whom TRAIL teams can build strong partnerships.

The pharmaceutical market. In 2007, the worldwide prescription drug sales grew 6.4%, reaching US$ 712 billion. The drug market for the US combined with Canada accounted for 46% of global sales (US$ 304 billion) with a growth of only 4.2%, while the market of 5 major European countries (France, Germany, the UK, Italy and Spain) grew 4.8% to US$ 140 billion. The pharmaceutical industry is characterized by a high level of concentration with fifteen multinational companies dominating the industry, among which Sanofi-Aventis in France, AstraZeneca, Novartis, Roche, Bayer and GlaxoSmithKline in Europe. TRAIL members are already engaged in collaborations or discussions with some of these leading players, and Sanofi-Aventis is one of the founders of the Fondation Bordeaux University. In addition, TRAIL can rely on the structuration of a health cluster in Aquitaine region (see section 4) grouping several actors in the field of biomedical development and covering the full value chain of drug development from the molecule to production.

In addition TRAIL will strongly contribute **to improving public health and costs related to health care** in a context where population is aging, and in a growing quest for wellness. Indeed, recent literature has showed that investment in biomedical research has driven huge socio-economics benefits: for exemple Johnston[1] reported in 2006 that 335 M$ invested in research trials by NIH yield new benefit for society after 10 years of 15.2 Md$ and Marescaux[2] report indicates that public spending in health research has a 25-40% return on investment per year. More generally, literature reports a return on investment in biomedical research for the society evaluated at least between three and eightfold, provided that all the dissemination and exploitation of results channels are optimized, that are 1) Increase in the stock of useful knowledge, 2) Supply of skilled graduates and researchers, 3) Creation of new scientific instrumentation and methodologies (including drug discovery process), 4) Development of networks and stimulation of social interaction, 5) Enhancement of problem-solving capacity, 6) Creation of new firms, 7) Provision of social knowledge.

TRAIL will thus implement innovative strategies for exploitation of its results aiming at optimizing all these exploitation channels. Based on the current activities of TRAIL partners, several priorities have been identified:

- develop an active policy for dissemination of knowledge aiming at **strengthening the regional, national and international leadership of TRAIL**. TRAIL Labex teams' excellence in research will allow them to write scientific publications, and to diffuse their results through the participation in regional and international events (Aquitaine Healthcare cluster events, international workshops,...);
- **filling the current funding gaps regarding technology and drug discovery development for transfer,** especially thanks to the financing by TRAIL of early stages of new technologies

[1] Johnston, S.C., J.D. Rootenberg, S. Katrak, W.S. Smith and J.S. Elkins (2006), 'Effect of a US National Institutes of Health programme of clinical trials on public health and costs', The Lancet, 367, pp.1319-1327

[2] Rapport de la Commission sur l'Avenir des Centres Hospitaliers Universitaires présidée par le Professeur Jacques MARESCAUX, Mai 2009

development (proof of concept) to allow more IP generation, and first stages of translational research;

- **intensification of the partnership with industrial partners** (devices, contrast agent, pharmaceutical companies, …) in order to enhance TRAIL capacities to bring research results to the market (medical devices, drugs) through additional financing of very costly clinical or development phases, but also through the access (thanks to the industrial partners) to know-how essential for anticipating the potential of development of our researches results and teaching activities for the economy.
- **providing a comprehensive organizational scheme for synergizing the academic, clinical and industrial research effort**, overcoming regulatory and institutional breaks/barriers, and accelerating successful research translation. Our aim is to offer a unique and highly visible gateway for communicating and interacting with other third part organizations including industries involved in biomedical research from drug discovery to clinical trials, national (ANR, PHRC) and international (PCRD, NIH) research and innovation (OSEO-ANVAR) funding agencies, as well as other academic partners.

5.2.2.1 Medical and industrial applications: Consolidation of existing collaborations

One main objective of our LabEx TRAIL regarding exploitation of our results is to **strengthen existing collaborations**.
By **sharing** industrial contacts, the labs get more collaboration opportunities, and the companies will benefit from a wider, coordinated offer from the TRAIL LabEx.
Targeted therapies and diagnosis guided by molecular imaging
This very promising project of stem cell-based therapy was supported by the European Excellence Network DiMI (Diagnostic Molecular Imaging), which will contribute to **promote industrial exploitation** of the results.
Local drug delivery, by encapsulation of active molecules with thermolabile liposomes.
A patent was filled in 2009 protects this discovery, as a joint invention with Philips in the collaborative European project SonoDrugs. **Philips is thus the selected** partner for exploitation of these results.
MR-guided thermal ablation of malignant tumors with HIFU. The commercialization of this product would represent **an important market for Philips Healthcare**. For the lab, clinical application of their investigations would represent a success story in translational research.
New biological markers developed in Klaus Petry's lab, may be of interest for pharmaceutical companies. In the case of **Merck Serono, this company will be the first served** if it confirms its interest for the thermosensitive markers.
New methods and contrasts for medical imaging in humans
The new methods developed in Jean-Michel Franconi's lab with industrial partners: **Brucker will be the first** to industrialize the newly developed prototypes if the results prove medical benefits.
Klaus Petry's team recently developed new site-specific contrast agents that can be carried by ligands that specifically bind either tumors, or sites of neuroinflammation. **Guerbet has contractually the right of first refusal** regarding exploitation of these results.
Michele Allard's develops and validates new radiopharmaceuticals, which will have direct applications in medical imaging. In the same way, **GE Healthcare has a "first right of refusal"** regarding the radiopharmaceuticals compounds developed by Michele Allard's lab.
Preclinical and Clinical Investigation
Preclinical and clinical trials represent the last two phases of our bench-to-bedside translational researche with the support of the Center of Clinical Investigation Pluri-thematic (CIC-P) and of the Clinical Research and Innovation Direction of the Bordeaux Hospital (CIC), in their interest fields: Neurosciences, Oncology, Chest Diseases, Cardiology and Nephrology.

5.2.2.2 New partnering approach

The TRAIL will offer better visibility to medical imaging research teams of Bordeaux, allowing them to attract new partners, academic as well as industrials. For instance, contacts are already engaged with some of the leading players such as AGFA Healthcare or Sanofi-Aventis. For the search of industrial companies, the ITEC CRO company (see letter of intend in annexe 7) is strongly interesting in participating to promote contact and contracts with their offer to help for setting up clinical researches. We will search as well an industrial partner in the field of informatics, in order to develop our mathematical modelling project. Given the very dynamic regional context for medical informatics industry, we are very optimistic to find future collaboration.

5.2.2.3 Pooling our Technology Transfer

In order to facilitate the setting up of new collaborations, we intend to pool our technology transfer means through a **single gate unit**.
For this purpose, we need to recruit a business developer (2011-2012) that will organize the one-stop service, will directly canvass industries and business offices, will display to the industries and private sector a good understanding of our researches and teaching activities. The initial salaries will come from LabEx funds to secure a non-tenure position for two years. After two years, in case of success, private funds should take over LabEx funds.

5.2.2.4 Protection of results

Today, the labEx teams have filed a total of 11 patents, and have operated 2 license transfers.
For example, GE Healthcare holds the intellectual property of the LOTUS technology, and GE will exploit the new improvements of the device; however the new radiopharmaceuticals developed in the lab will belong to the sole public institution. If new diagnostic tracers and methods are validated, GE healthcare will likely commercialize these solutions, arguing of its first right of refusal.

5.2.2.5 Impact on national and international regulations and guidances

TRAIL LabEx will improve the international visibility of Bordeaux medical imaging research. Together with their partners, among which the CIC-EC, TRAIL members will design and validate new imaging protocols to improve diagnosis in a cost effective way. They will also contribute to advances in clinical research and drug development by validating new biomarkers that could be used as surrogate markers in clinical trials.

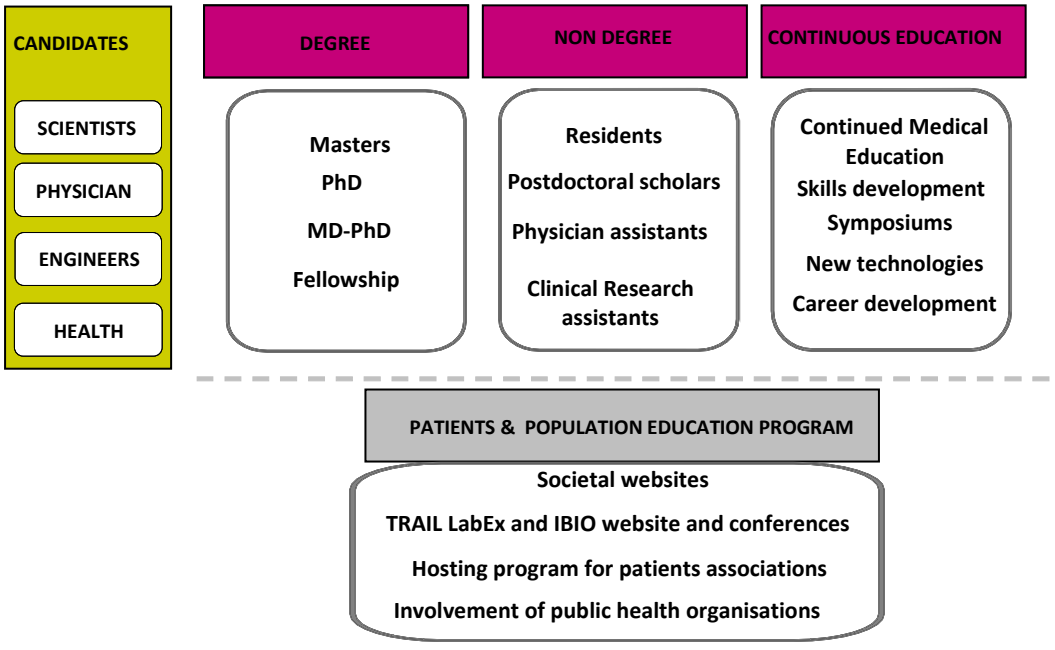
Higher education, Integration into the workplace

The Educational Project of TRAIL Labex
Dissemination of new information and knowledge

Innovative translational research in such a multidisciplinary field as bio-imaging requires the teaching of bioengineers, scientists and medical students in diverse domains. As technical medical practice and health care delivery have grown in complexity, training requirements are also increasingly specific. Moreover, there is a need to better inform patients and the general public in order to further improve the outcome of innovative treatments.

The educational programme of TRAIL will be coordinated by Professor JM FRANCONI, current director of RMSB (Partner 3). The participants include 62 university professors who are actively involved in teaching activities within their respective schools of medicine, biology, mathematics, physics and chemistry, as well as full time researchers. At the doctoral level, the implication of the IBIO-TRAIL Labex project is assured by the fact that a board member (Pr Franconi) will be a member of the Doctoral School comprising approximately 70 graduate students in the different research laboratories participating to the project (including international MDs).

Overview of the different initiatives for education that IBIO-TRAIL LabEx will have in charge:



The teaching program is organized as described below :

Degree program for medical, engineering and science students

MD-PHD PROGRAM:

A joint M.D./Ph.D. program, restricted to a limited number of candidates combining medical education with the best research environment, is presently offered by the Doctoral School in partnership with the Teaching Hospital. The goal is to train future leaders to work at the interface between science and medicine in order to continue their career in our Institution or elsewhere. An expanding part of this MD-PhD program will be to educate candidates to develop new scientific insights that lead to innovative translational strategies from basic sciences or advanced imaging knowledge to medical fields such as Oncology, Neurology, Cardiology, Pneumology and Nephrology.

TEACHING OF ENGINEERING AND SCIENCE STUDENTS THROUGH THE INTERNATIONAL MASTER IN BIO-IMAGING

The LabEx will foster the development of the International Bio-Imaging Master of Bordeaux, starting September 2011, exclusively taught in English in order to be internationally attractive and to prepare students for mobility while reading and working in English. Several of the teacher-researchers (professors, associate professors) of the IBIO Institute and the LabEx project participate in the masters teaching in addition to their participation in several other master courses and teaching at the medical school. Based on annual calls for mentoring programs and interdisciplinary collaborations (such as developing skills for writing papers, teaching, publication strategy, setting up interdisciplinary seminars and workshops with international guests speakers, …) we will offer a broad and diversified range of learning activities.

A special focus on the International Bio-Imaging Master is given in Annexe 7.7.3

TRAINING OF STUDENTS IN SCIENTIFIC RESEARCH

The pan-university education and research organization (PRES grouping Universities of Bordeaux) already offers a variety of courses, organized as part of its Licence-Master-Doctorate program. The Master level, within the domain of "Health and Biology" (evaluated A by AERES) include specialties such as Bioimaging, Cell Biology and Pathophysiology, Biomaterials, Neurosciences that propose training in imaging, while the domain "Drugs and Health products", "Computing" and "Mathematics" also propose relevant training. At the doctoral level, laboratories involved in the IBIO institute-TRAIL LabEx program belong the Doctoral School "Health and Life Sciences" (evaluated A+ by AERES).

In addition, specific more "job-orientated" courses will be organized to prepare students for future job opportunities that will be generated in the field.

We wish to develop PhD student stipends through an annual call. This action will allow our own selection of PhD students that will include a pre-selection of the projects submitted and an oral examination of the pre-selected candidates. Finally, we will encourage the participation of the private sector (industries, CRO, associations of patients, etc) to teach in Masters or PhD degrees, to offer internships and to financially support the calls organized by the LabEx.

Non degree programs

The residents in radiology and nuclear medicine, the residents of cardiology, neurology, oncology, pneumology and nephrology and the residents in public health (who do not enter a complete MD PhD program) will be offered the opportunity to have training in research (e.g. at the masters level, with at least one semester during their internship in the research laboratories of the TRAIL-LabEx in order to have first-hand experience in the above fields).

Post-doctoral stay in foreign laboratories will be proposed to qualified M.D-.PhD or PhD doctors.

Translational Clinical Research Assistants will be able to participate in pre-clinical and clinical teaching and research, in the field of translational imaging through the non degree educational program of TRAIL LabEx.

Continuous education

The field of bio-imaging is changing very quickly (see section 5.1 State-of-Art) and medical applications are evolving in many directions. The need for continuous education is therefore extremely intense. It should be noted that numerous scientific societies are offering annual educational courses, to which many of the TRAIL LabEx professors and researchers are participating (see section 4.2.4) at national and international levels. However, updating one's knowledge often require course of a longer duration and more specific focused. The RMSB has been proposing for ten years an annual continuous educational program on MRI physics and biology and health applications. Based on this successful experience, the TRAIL LabEx will organize courses for Scientists and Engineers from public or private companies and will promote continued medical education courses.

Patients associations and Society

We intend to develop a detailed Web site of our IBIO-TRAIL LabEx. Full information about trends in Bio-Imaging and medical applications will be given and up-dated (action 1). Considering that public money will be engaged through the LabEx call and also to give the population a better general feeling about research and scientists, we also want to inform the public on the development of our translational research through dedicated web site pages (action 2). Finally, supportive structures, selected patients

associations, and industries engaged with us will have special access to the most innovative research and to our works-in-progresses (action 3).

Solutions of funding through the Foundation of Bordeaux University (a support structure of the LabEx) are offered to industries. Recently we obtained a 350.000 euros private grant from a radiological association for education in the field of Bio-Imaging. Our IBIO Institute and LabEx project has also raised funds with a recent engagement of the AGFA company (see letter of intent in annexe) with an initial investment of 240.000 euros dedicated to promoting education and research. The LabEx funding support will strongly boost the different educational programs and actions detailed above.

Basics of Governance of TRAIL

Governance and management principles

The form of governance within the LabEx TRAIL reflects the overall objective of the partners involved, i.e. to collaborate constructively with a view to promoting rapid growth over the next three years and to keeping with a long term shared strategy. It is organized with the following aims in mind:

- To be flexible, professional and responsive;
- To ensure the successful integration of TRAIL projects into its scientific and strategic environment at the local, national and international level, without creating additional layers of responsibility, and in keeping with the strategy and prerogatives of its reference organizations and partners;
- To establish rigorous monitoring of how resources (financial, human, platforms, etc.) are used and how TRAIL objectives are attained;
- To promote effective communication between the TRAIL partners.

Within the framework of the *Investissements d'avenir*, the University of Bordeaux is acting as the coordinating partner for all the projects submitted by its members, so as to ensure consistency and synergy between them as well as their full integration in the overall strategy set out by the University. The University of Bordeaux will manage the funds coming from the ANR for the development of TRAIL and will take the responsibility for the proper monitoring of resources before the ANR, as defined in the convention attributive. The University of Bordeaux is one of the leading campuses in France for research and education, comprising 4 universities, 2 schools of engineering and a school of political science. It comprises more than 5 000 academic staff and around 60 000 students (including 3 000 PhD candidates). With an annual budget of 6 Md€, it has proved its capacity to manage funds according to high standards of quality and efficiency.

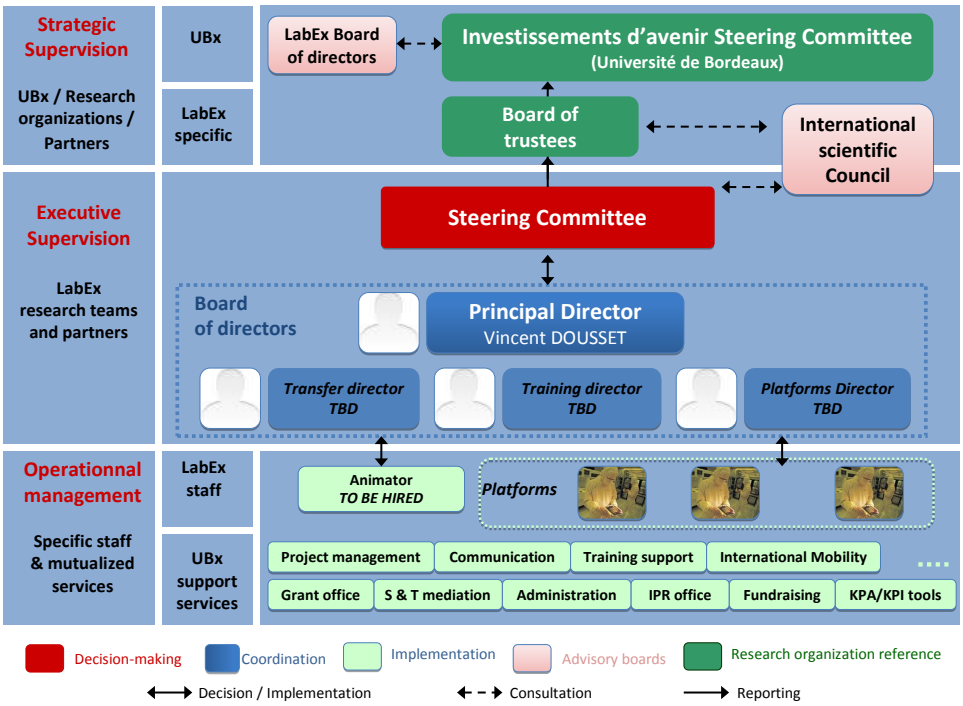
Governance structure

TRAIL will not be incorporated formally as a legal administrative structure and will be a light structure **running on a project mode**. Its governance will thus reflect this mode of running and will be close to the one that has been efficiently used by several thematic research networks (namely RTRA) in France and has proved its adequacy with the specificities of the national organization of the public research.

The governance structure of TRAIL comprises **a board of trustees**, a **scientific council** and a **steering committee**. Members of these boards represent the founding institutions of the TRAIL and the scientific partners. Stakeholders will endorse a consortium agreement on the LabEx TRAIL that will establish its objectives and the means allocated by the founding institutions to attain them. This consortium agreement will apply for a given period of time (based on the terms set out in the agreement drawn up with the ANR in order not to duplicate efforts) and be subject to annual evaluation.

Board of trustees

The **Board of Trustees** will come under the aegis of the *Investissements d'avenir steering committee of the University of Bordeaux,* which is responsible for supervising all the *Investissements d'avenir* projects selected in Bordeaux and for approving TRAIL strategy for growth. The Board of Trustees thus is in charge of assessing the administrative, budgetary and financial actions proposed by TRAIL and that will be specified in the consortium agreement. The board will comprise all the parties (research bodies, industrial partners, regional government, etc.) whose interests are represented within TRAIL. The board will meet at least once a year in order to assess the progress of TRAIL towards achieving the agreed objectives and review the terms of the consortium agreement.



The annual performance review of the TRAIL will assess four Key Performance Areas underpinning its programmes (research, training, transfer), including mesures of the following : **Activities** (actual realization of the annual action plan), **Outcomes** (actual outputs of the LabEx), **Leadership** (actual visibility of the LabEx), **Ripple effect** (actual impact of the LabEx on the overall development plan of the University of Bordeaux see section 3). In the event those objectives are not being met, the board of trustees will ask *the steering committee of the LabEx* to propose corrective actions.
Given that the board will also be in charge of facilitating external relations between the TRAIL and national or international networks, it might include persons qualified for this purpose.

Steering Committee

The steering committee **is the upper board of the LabEx** TRAIL, and its members represent the research laboratories comprising TRAIL. The committee will meet on a 2-monthly basis to discuss the growth strategy for TRAIL and to implement the general guidelines approved by the board of trustees. It makes decisions on the basis of joint initiatives put forward by the partners of the TRAIL, with particular focus on those initiatives to be funded from its own resources. It also monitors the progress of scientific transfer and training projects.
For the daily running of TRAIL, the steering committee will appoint a executive body called the ***board of directors*** composed of a director in charge of implementing all the aspects of TRAIL scientific programme. He/she will also chair the steering committee and three assistant directors in charge of technology transfer, training and technological programmes. Each of these directors will run thematic working groups that will regularly discuss projects initiated by member laboratories, the best practices that could be shared between members, and other opportunities.

Scientific Council

The members of the **Scientific Council** are all highly qualified international academics working in the research community. They will meet annually to discuss the overall policy of the TRAIL for the coming years and to assess the annual scientific programme. The council also will play an advisory role regarding the scientific policy and activities of TRAIL.

Operational structure

Research, training and transfer activities related to the programs financed on the LabEx funds will be performed either by temporary staff (such as Ph.D fellows) or by the personnel of the partners constitutive of the LabEx, that will be made available on a project mode, for a given period. These activities will thus be held in the premises of each partner and with respect to the internal regulations of each research laboratory or hosting institution.

This organization **on a project mode** will be supported by an operational slight structure for the LabEx will be settled up and mainly include a programs manager hired on a contractual basis who will support the board of directors regarding the daily management of TRAIL activities and the implementation of TRAIL programmes.
Several professional service will be provided by the University of Bordeaux as shared resources for TRAIL such as communication, financing, project management, fundraising, IPR advice, etc.; Occasionally, some other resources of the main partners (research laboratories) or other associated partners (transfer units, etc.).

The aim of this form of organization is to utilize efficient professional dedicated human resources, while optimizing financial resources. Alleviating the administrative hurdles for scientists involved in running TRAIL will also be a key issue.

Attraction

The TRAIL LabEx project will address the major issue of attractiveness to the French research environment. One of the major target will be to attract new teams of researchers. Since his constitution as an Institute of Bio-Imaging in 2007, two teams of researchers have join the IBIO: Dr Yannick Cremilleux PhD from Lyon (Pr P. Berger Team), a leading specialist on lung imaging and the famous team on neurofunctional imaging from Caen (GIN, Pr B. Mazoyer Team) with twelve researchers.
The TRAIL Labex will work on:

- Attracting young MASTER students (both French and International)
- Selecting PhD students
- Attracting selected high-level researchers, in order to boost the scientific strategy of TRAIL;
- Attracting industrial companies by a mutual understanding an by offering one-stop solution for the entire TRAIL LAbEx, directly or through the Foundation University of Bordeaux.

The attractive strengths of TRAIL:

1. **Funding Capabilities**
   a. From the LabEx budget through annual calls for research projects: 3 annual 160 k€ and 4 annual 50 k€ LABEX GRANTS for financing post-doctorants and engineers, equipements and running costs
   b. Possible financing with industries through the Foundation University of Bordeaux
   c. Assistance for « call for proposals » participations (FP7, *etc.*) by the UBx Grant Office
   d. Assistance within the LabEx for partnership with private corporates (contacts and contracts)
2. **A New Organization that fosters Translational Research on Bio-Imaging**
   a. With eight support service structures,
   b. In close collaboration with French major University Hospital and Cancer Institute,
   c. In the setting of an "operation campus financing"-selected University.
3. **A high Scientific Environment**
   a. Eight teams of cutting-edge imaging researches
   b. Ten well-identified collaborating and challenging research groups with ripple effect on other major labs of Bordeaux University
   c. A scientific governance, including an International Advisory Panel
4. **An Education Directly Oriented to Bio-Imaging (see section 5.2.4 Higher Education)**
   a. A New International Master in Bio-Imaging exclusively taught in English with a multi-disciplinary education (see section Higher Education 5.2.4 and Annexe 7.7.3)
   b. Annual Scientific animations with specific workshops organized by the communities of TRAIL
   c. Stipends for PhD Students: TRAIL will recruit and give grants to 12 highly selected PhD Students
5. **A large Working Space (see section 5.2.1 Scientific Program)**
   a. We offer 7500 m2 of renovated laboratories (operation campus) and large hospital facilities for clinical researches
   b. We are building a 3000 m2 new facility for the IBIO and TRAIL LabEx; 1000 m2 are dedicated to welcome the next new teams.
6. **A state-of-the-art technological Imaging Platform (see section 5.2.1 Scientific Program)**
   a. A pre-clinical and clinical platform has the highest French quality standards (IBISA platform),
   b. Large variety of developed animal models,
   c. With expecting new equipments via EquipEx call (microCyclotron and MicroTEP/CT/MRI; Interventional Cardiac 3T MRI) and InfraStructure National call (Human 7.0 T MRIand Pre-clinical 7.0 T MRI) (see section 2 – Calls in Investissements d'Avenir)
7. **Quality of Life in Bordeaux**
   a. A large eighteen century city surrounded by wineyards in the South West of France (ocean and mountains)
   b. With a french major International Airport.

Strategy of the supervising institution

The University of Bordeaux has set out on an ambitious process of transformation based on its strategic plan adopted in 2008 and entitled "Towards a new university model". Its main objective is to reorganize research and teaching activities around internationally visible ***pôles d'excellence*** and to play an ever stronger role in the socio-economic dynamics of Aquitaine and France. Thanks to this strategic plan, the University of Bordeaux was chosen in 2008 to become one of the first ten sites in France to receive funding (total of 545 M€) for renovating its campus (*Opération Campus*).
The University of Bordeaux now wishes to seize on the opportunity of the national ***programme investissements d'avenir*** to reaffirm its commitment to this strategic plan and to accelerate its development.

The objective of the University of Bordeaux is to consolidate its current position so as to become one of the 5 to 10 world-class French centers of excellence for research and education, contributing to make Bordeaux one of the most attractive cities in Europe.

By achieving this, the University of Bordeaux will contribute to reach the goals set in the national strategy underlying the development of the programme "investissements d'avenir":

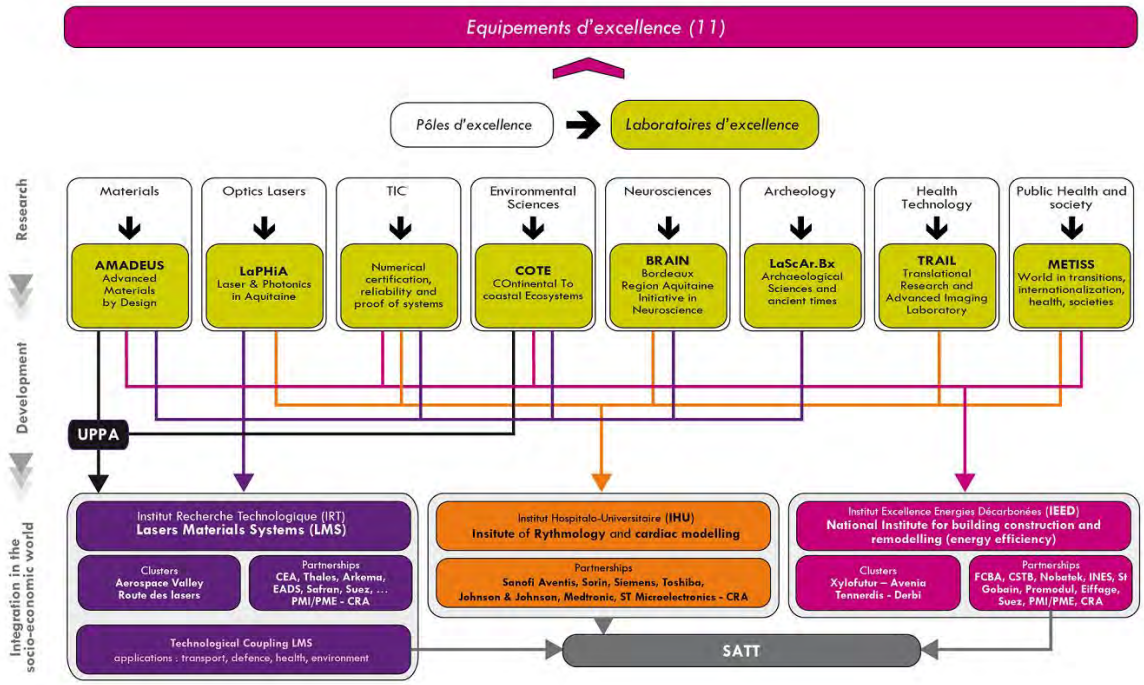
- the international influence of France in research and higher education, with the aim of getting the University of Bordeaux into the top 100 universities in the world (Shanghai ranking or equivalent);
- growth through innovation, so as to place Aquitaine in the category of "high innovation" European Regional Innovation players ("High innovators" category of the Regional Innovation Scoreboard - RIS);
- the sustainable renewal of the regional, national and European economy, with the objective of specializing the University of Bordeaux to operate in markets with high added value and strong growth prospects.

These ambitions have led to the creation of an ambitious program of development to be presented during the various calls for investment in the future and which is built on the following principles:

- Strengthening the core elements of the knowledge / diffusion / transfer cycle in order to optimize the value chain;
- Choosing research themes with high added value and high capacity for dissemination;
- Making sure projects receive controlled funding from the first euro spent.

The LabEx policy at the University of Bordeaux

The "laboratories of excellence" (LabEx) projects are playing a major role within this program of development as they are meant to become the driving force for the strengthening of the ***pôles d'excellence*** defined in its strategy. While they may play such a role, the scope of action of the LABEX projects is narrower than that of the *poles d'excellence*.



The University of Bordeaux conceives a laboratory of excellence (LABEX) as a grouping of research teams whose excellence is widely recognized (within the terms of the discipline concerned), who have wide international visibility and who are willing to contribute to an ambitious innovative research project whose prospects for valorisation of the research are important, whether in terms of image for research in France or in socio-economic terms (development, training).
From an organizational point of view, a LabEx is a light structure with no legal administrative structure and is running on a project mode. The funding of the LabEx will be used to promote research, training and transfer programmes related to priority axes defined by the stakeholders of the LabEx as a common space for collaboration.
Partners involved in the LabEx are, for the wide majority, research teams located in Bordeaux, but may also be research teams based elsewhere in France having a complementary competency necessary for the project. The governance structure of the LABEX comprises a board of trustees whose members represent all the reference research organizations of the research teams involved.

The objectives set by the University of Bordeaux for each LabEx project are

1) to be among those who are doing the European research agenda;
2) to set off a ripple effect for the relevant *pole d'excellence*;
3) to promote the development of new interdisciplinary methodologies.

The University of Bordeaux is therefore presenting 8 LabEx projects that meet these specifications and which are all fundamental pillars of its policy.

University of Bordeaux as coordinating partner

The University of Bordeaux is thus acting as the coordinating partner for all the projects submitted by its members, so as to ensure consistency and synergy between them as well as their full integration in the overall strategy set out by the University. Most of the research labs in Bordeaux and the Aquitaine Region – and generally in France - come under the scientific auspices of at least two research organizations and sometimes more, one being a university or an engineering school, the other being a national research organization such as **CNRS, INSERM, INRA, INRIA, CEMAGREF or CEA**. So as to ensure local consistency and full integration of all the projects in the strategic plan, these research organizations have agreed to sit as members of a Technical Committee (COTEC) in charge of the overall supervision of all the *Investissements d'avenir* projects proposed by the University in Bordeaux.

Thus, all academic parties, i.e. the public partners, involved in the current project are kept fully informed about this request to the ANR within the LabEx framework. This dynamic will be continued in the future and each of these national research organizations will be part of the "Investissements d'avenir Steering Committee" of the University of Bordeaux (see section 5.2.4 for the description of the governance).

Connections to the socio-economic world

As explained in the 5.2.2 section, the TRAIL LabEx is deeply engaged in the diffusion and transfer of the results of its research to the socioeconomic world. Member teams are already involved in several successful initiatives in this direction, as shown in the 4.1.2.2 section. Its vocation is to be fully opened to the socioeconomic world.
We will then foster the development of collaborations with other academic partners as well as industrials. We will also give the Bordeaux research and industrial community access to our skills and our state-of-the-art technology platform.

We want our work to provide results that can directly beneficiate the patient and the society as a whole. For us, in order to fulfill our mission, **the key is to be deeply interconnected with our socio economic environment.**

We see **3 major challenging domains of application for medical imaging today to improve patient care:**

- diagnosis
- personalized medicine: treatment follow-up and image guided therapy
- drug development: providing surrogate marker

Our work will lead to applications in these three domains.

The existing industrial collaborations show that the various teams composing our TRAIL LabEx already have an important impact on the development of imaging systems, including imaging sequences and methodologies, development of new contrast agents and radio-markers, as well as new imaging devices and equipments. In addition to these traditional partnerships with the Imaging industry, there is a growing interest of pharmaceutical industry for imaging.

Indeed, medical imaging has become a significant and useful tool for use in preclinical and clinical trials, enabling rapid diagnosis from visualization and quantitative assessment. While non-invasive imaging came to prominence initially as a diagnostic tool, the last decade has seen rapid advances in translating traditional diagnostic methods to enable imaging of functional, physiological and molecular processes, thanks to the development of biomarkers.

Biomarkers developed and validated in the TRAIL LabEx teams potentially enable non-invasive means of assessing mechanistically and clinically relevant properties of many diseases including cancer, atherosclerosis and other cardiovascular diseases, neurodegenerative disorders and other inflammatory diseases, lung as well as kidney diseases. Imaging biomarkers include any anatomical, physiological or molecular parameter detectable by one or more imaging methods, and are used to establish the presence and severity of disease.

While discovery of promising biomarkers is the initial critical step in the process of imaging biomarker introduction, equally important is the development and validation of the biomarker, which can occur only through rigorous testing and broad application in disease models. The constitution of the TRAIL LabEx aims at facilitating this validation process and acceptance of the biomarker for use as a surrogate marker- a biomarker that can be used as a substitute for a clinically meaningful disease end point.

As increasing numbers of reliable image-based biomarkers will be developed and, importantly, validated and qualified, the opportunity for developing effective therapeutics will increase through enabling of more informed decisions at earlier stages in drug development. This will result in a high number of applications in the process of pre-clinical and clinical development, and will very likely reinforce existing collaborations with pharmaceutical companies (Merck Serono, Novartis) as well as create new collaborations. For instance, Sanofi-Aventis is currently evaluating the possible

collaborations with our future TRAIL LabEx. In an industry where appropriate early decisions drive efficiency and success, validated, translatable disease-relevant biomarkers are invaluable.

We are aware of the continuous increase in healthcare costs and the need to rationalize expenses. This is why we will focus on medico economic evaluation of the innovations we are developing. Medical imaging can be very expensive. Yet, it offers unique opportunities to improve diagnosis and treatment that can lead to subsequent dramatic savings. We will not only work on the development of new tools and protocols, but also on their integration in global healthcare and their cost effectiveness evaluation.

Pull effect

Adding a new dimension to the IBIO, the LabEx TRAIL will represent a major asset for Bordeaux area, contributing to its dynamism beyond the results of its biomedical research.

Pull effect on the regional academic research

Beyond the partner teams that compose the LabEx TRAIL, this initiative will positively impact all teams of the partner labs. Altogether, this represents 500 persons among which 350 full time staff. It will offer them new opportunities in terms of access to skills and tools for conducting their research, possible collaborations, but also in terms of exploitation and diffusion of their results, by working in close contact with LabEx member teams.
Beyond the LabEx partners, the collaborators and supportive structure will beneficiate from the positive impulse generated by the LabEx. Research conducted in the LabEx will provide them with new projects, generating an increase in their activity, with a consecutive increase in their competency and the need for recruiting new staff. This will allow them to expand. For instance, the CIC-EC will contribute to the medico economic evaluation of new imaging methods developed within the LabEx. It will by this way gain expertise in this field and will be able to extend its offer towards potential clients. The LABRI and INRIA will work on several projects with the LabEx on numerical models and image processing. This will extend their expertise in medical imaging application, and will give an opportunity to set up a dedicated team in medical image processing in Bordeaux. This is indeed one of the top priorities of our LabEx TRAIL to be able to complete the value chain of medical imaging development in our region, by attracting this only missing part today that is a dedicated team on medical imaging processing.

Pull effect on the regional industry

The LabEx TRAIL will offer an easy access to its state of the art technology platform for local industrials, whatever the state of development of their product. We will be able to answer all their needs by providing a global service, including appropriate skills together with access to specific equipments. By being able to easily test their products, they will be allowed to save time and money in product development. As many of them are SMEs, this opportunity will also allow them to engage with more confidence in bigger projects.
For instance, CEVA laboratory, an industrial group specialized in animal health whose headquarters are near Bordeaux, has already expressed its interest in the service offered by the TRAIL platform.
In addition, our biomarkers could also be of use for regional drug development SMEs, through drug targeting. Indeed, several companies specialized in galenic formulation are located in Aquitaine region: Galenix, Unither développement, Physica Pharma, Flamel Technologies, Ellipse Pharmaceuticals, IDPS work on all aspects of better targeting drugs to specific sites. We aim to achieve one or more collaborations with a regional drug development company.

Attractiveness of Bordeaux area in biomedical research and expected impact on local and national economy

As described previously, the regional Healthcare industry strengths are mostly concentrated in three areas: drug development, implantable and non-implantable medical devices, and medical informatics. The reinforcement of research in medical imaging through the LabEx TRAIL will encourage the development of companies in this area, completing the scope of local healthcare industrials, as demonstrated by the spin-off Image Guided Therapy.
Academic biomedical research in Bordeaux area is also famous. Nevertheless, its expertise in medical imaging is not obvious enough today. The TRAIL LabEx will contribute to its higher national and international recognition.
This will have several effects on the dynamism of the region Aquitaine:

- Together with the IHU LIRYC projects (in electrophysiology) and other academic research projects, our LabEx will attract new research teams and researchers in Bordeaux, which means high income newcomers that will settle and contribute to local economy.

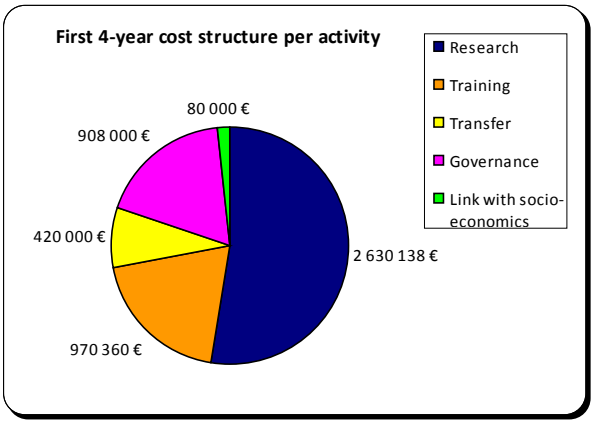
- The availability of expertise in medical imaging will attract new collaborations with academic as well as industrial partners worldwide, new projects which will contribute to the development of local activity.
- This will also be a major asset for attracting clinical trials: by offering a global service including surrogate markers and imaging tools, Bordeaux area will be the place of choice for major clinical trials sponsored by multinational companies.
- This growing implication of Bordeaux area in drug development will feed local industries specialized in drug development, in particular in galenic formulation, with new projects.

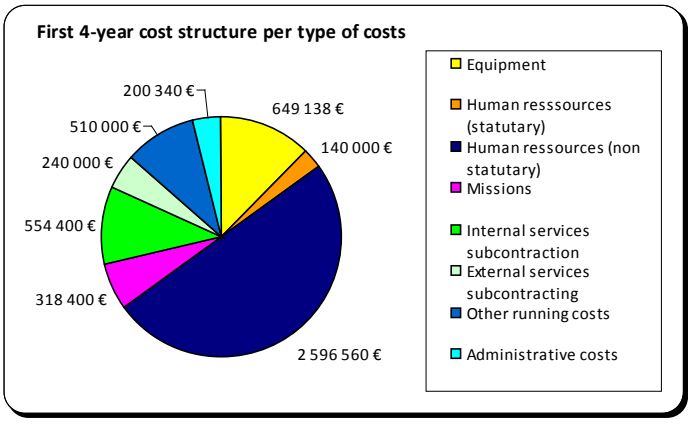
Despite excellent academic research in medical imaging, France today stands behind in terms of development of medical imaging industry. This area is mainly driven by SMEs, and some R&D implantations of leading multinational companies like GE or Philips. In order to capitalize on this strength of French R&D, an effort has to be made on helping the transfer of results of academic research to industry. This has been emphasized by the French Ministry of Industry among the "Key Technology for 2015". The creation of our TRAIL LabEx and its great interconnection with its socio economic environment is an important step towards the improvement of French competitiveness in this strategic area.

Financial and Scientific justification for the mobilisation of the resources

05/

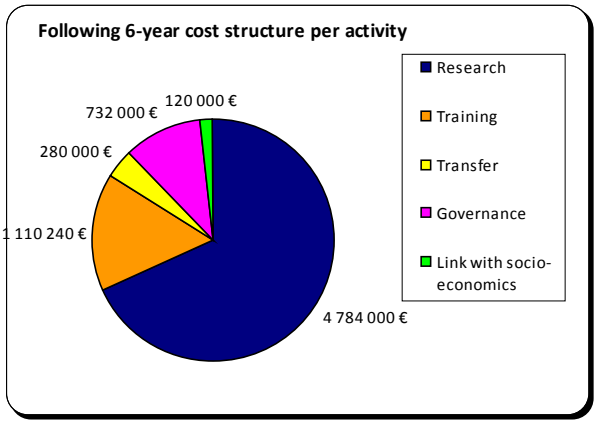
The total amount asked for the LabEx TRAIL is **12 516 128 €** over ten years. It covers all of the costs mentioned in this section (6.1) as well as a 4% administrative charge. The funds will concern investments for research, education, governance and links with socio-economics and will be distributed as shown hereunder.

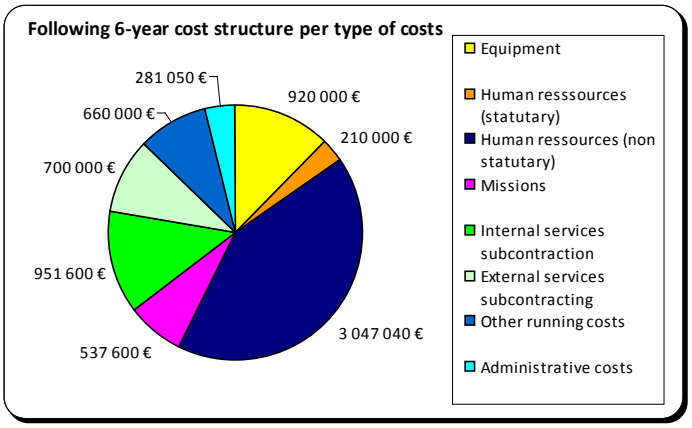




Total cost of 5 208 838 € for the first 4 years of activity that is an average of 1,3 M€ per year

Total cost of 7 307 290 € for the following 6 years of activity that is an average of 1,2 M€ per year





Justification for the mobilisation of the resources

Financial resources of TRAIL will be dedicated to several types of actions:

- funding of structuring programmes to develop activities of TRAIL;
- funding of common infrastructures (equipment, computing facilities, etc.);
- funding for the development of individual skills of TRAIL actors;
- funding for strengthening the life and the visibility of TRAIL,

and focussing on several objectives:

- **Attract**, outstanding external scientists, students and additional funding (private, public);
- **Growth**, by producing useful knowledge, methodologies and problem solving capacity at international level of excellence
- **Value** creation, by increasing the exploitation of results produced by TRAIL including the supply of skilled graduates and researchers
- **Leadership** of TRAIL in its field at the regional, national and international level.

Funds will essentially be managed through Calls for projects and following the same selection structures, so as to ensure strategic coherence among them. The Board of directors will set up and run the different calls on the behalf of the Steering Committee, and the selection process will include international expertise.

Structuring programmes	Research project	Educational project	Exploitation of results	Governance
Incentive programme for new research projects	Growth Attract			
Grants for translational research	Growth		Value	
Business development capacity			Value	Leadership
Common infrastructures	Research project	Educational project	Exploitation of results	Governance
Imaging Data Centre facilities	Growth Attract	Growth Attract	Value	
Research equipment				
Video-visio conference equipment for remote teaching		Attract Growth		
Development of individual skills				
Mentoring programs (Master and Ph.D)		Value		
Master internship		Value		
Doctoral grants	Growth	Value		
Strengthening the life of the LabEx				
Research Seminars with invitation of International Renowned Professors	Growth Leadership			
Seminar on training objectives with invitation of key note speakers		Growth Leadership		
Grants for the mobility of TRAIL actors	Leadership			
Permanent structure and running costs for the LabEx	Growth Attract	Value	Value	Leadership

*Details of the type of funding and related objectives by type of component of the project (in **strong** the section were the action is described in the following chapter).*

As shown on this table, some actions are targeting both research and transfer (due to the intrinsic character of translational research), or research and training, but for simplicity reasons are described hereunder only once.

Research project

TRAIL has defined **three main goals** to enforcing our collective capacity for research:

- **To enforce our fundamental imaging science**

We have determined seven work packages that will be applied to five medical fields. The eight partners of TRAIL are working with several collaborators from the Bordeaux University.

- **To reduce obstacles to translational research (T1) from bench to bedside**

We will move forward our researches to the clinical applications. This will be possible with the organization of several support services that do exist in the Bordeaux environment of TRAIL. In addition, we aim at evaluating the clinical impact and the decision-making approach of our researches.

- **To study the impact of our research (T2), new methods and new imaging technologies on clinical trials, personalized medicine, patient care, epidemiology and socio-economic impact**

↘ Action type : Structuring programmes

In order to achieve this, TRAIL will fund several structuring programmes that will be operated thanks to **calls for projects** that are the core of the structuring tools of the LabEx and are representing the main bulk of the LabEx research funding envelops. Each of them will therefore be focused on one or more themes among strategic priorities of the LabEx work packages. These calls for projects will also be used as a tool for attracting new teams in Bordeaux. Projects will be expertise and ranked by an international panel chosen by two international experts from our advisory board.
Two work packages, WP3 Dynamic Nuclear Polarization and WP6 Mathematical Simulation, are emergent and risk taking. We agreed already to prioritize the first call (2011) for these two projects.
The five other WP, are more advanced however they need to be boosted for increasing cooperation among different teams and disciplines, and for the translational process in order to be applied to humans.
Two types of packages will be available thanks to these calls for projects, mixing several types of eligible costs (manpower, equipment, missions, etc.) in order to keep the necessary flexibility over the time.

- **TRAIL Incentive programme for New Research Project**, will encourage new or risk-taking research projects, in relation to the Work Packages described chapter 5.2, jointly supported by eight teams of LabEx and also cooperation with research teams from other (international) universities. This is one of the actions to boost attractiveness. For an example, international researchers may be helped to settle at the IBIO institute by getting such of starting grant including a salary for a post-doctorant. Beside salaries, costs to settle might be granted trough this type of grants. In addition, the evaluation will prioritize projects that will search at finding solutions for T1 and T2 translation. This will be stimulating for starting new positions. However, the LabEx will not support long-term salaries and researchers will search for other calls or for tenure positions.

  An allowance of 130.000 euros will be available for each programme for:
  Personnel Costs: Minimum required 1 post-doctorant: 45.000 euros/an
  Other costs: Equipments – Subcontracting – Travel – Expenses for Inward billing – Other working costs: flexibility in the amounts according to the project. This may include publication costs (other costs), infrastructures costs for performing research (internal billing) and external services costs for computer programming.
  Three (3) packages will be available per year during the first 4 years, and then an additional package will be available per year starting in 2015 corresponding to an expected increase regarding the attractivity of TRAIL for external researchers.

- **TRAIL Contributing Grants For Translational research,** to boost translational research. Co-financing from other calls (ANR, FRM, FDF, Region Aquitaine, privates funds, industries and private companies participations, …) will be strongly encouraged for getting the grants. Getting this grant the following years after being granted for a research project in order to foster the translation of the initial research will be possible.

  An allowance of 50.000 euros will be available for each programme for:
  Personnel Costs - Equipments – Subcontracting – Travel – Expenses for Inward billing – Other working costs : flexibility in the amounts according to the purpose. This may include promotion costs or professional services cost for project management, quality insurance, etc. (external or internal subcontracting).

  Four (4) packages will be available per year during the first 4 years, and then an additional package will be available per year starting in 2015 corresponding to an expected increaser regarding available results for translational phases.

➘ Action type : Common infrastructures

- **Recurrent costs for using and implementing the Imaging Data Center**
  Population imagery requires tremendous amount of storage space and heavy computing means. In order to develop common secured procedures within TRAIL and encourage the sharing of data, TRAIL will offer storage and computation facilities. The costs for these facilities has been estimated up to ***50.000 €*** per year.

- **Shared Equipments for LabEx partner Teams.** TRAIL will finance some specific equipments identified as being of particular importance for its structuration.

Peptide Synthesizer for Work Package WP 4, Tracers and Contrast Agents and interactions with Oncology, Neurology, Cardiology, Pneumology and Nephrology: 63 000 €

Intravital video microscopy for intravital videomicroscopy of blood brain barrier alterations confirming experimental targeting before transfer to clinical research (WP 5) 240 000 € (co-financing resources 60% CR Aquitaine/ANR) = 96 000 €

HPLC analytic system = 62 790 €

Estimates are available in Annex 7.3

A cost of 30 000 € per year is planned for maintenance costs.

➘ Action type: Strengthening the life of the LabEx

- **TRAIL Research Seminars with invitation of International Renowned Professors,** TRAIL will finance some specific the organization of seminars for the partners, collaborators and support services (around 250 persons) on Progresses in TRAIL Labex

The average cost for one seminar is estimated to 10 000 € including

Organization costs subcontracted to external specialized company for 5 000 €

Invitation of 2 International Renowned Professors for 4 days
(two to three working days) ***5 000 €***
It is anticipated to organize **2 seminars per year** during 10 years

- **12 - Grants for the mobility of TRAIL actors,** in order to promote the participation to International Meetings – Workshops – Seminars for either statutory researchers or Ph.D students
  The average cost for one travel is 2 500 €, and it is planned to fund 10 travels per year (over a total of 189 members of TRAIL in 2010)

Equipment	Personnel cost statutory	Personnel costs (non statutory)	Missions	Sub-contracting (internal)	Sub-contracting (external)	Other running costs
TRAIL incentive programme for new research programmes						
720 k€		Post.Doc: 1 620 k€ 36 person (432 pm)	180 k€	720 k€	540 k€	90 k€
TRAIL Contributing Grants For Translational research						
400 k€		Post.Doc: 1 170 k€ 26 person (312 pm)	140 k€			180 k€
Computing and dataware house facilities						
				500 k€		
Shared Equipments for LabEx partner Teams						
434 k€						270 k€
TRAIL Research Seminars with invitation of International Renowned Professors						
			100 k€	100 k€		
Grants for the mobility of TRAIL actors						
			250 k€			

*Details of the funding requested linked to the research project per type of cost: total cost for the programme is estimated to **7,4 M€** for the 10 year period. Person.month (pm)*

Educational project

TRAIL has defined one main goal to **promote education for appropriate job qualifications and better social integration.**
Due to his multi-disciplinary and interdisciplinary setting, TRAIL aims at proposing new topics and new organization of teaching, either in the academic setting (licence, master, doctorate) or in continuous education. This will offer to students new job opportunities with perspective of doing research or to join the commercial and development of medical industries devoted to imaging.

Action type: Common infrastructures

6 - Video-visio conference equipment for remote teaching for a total costs of 15 000 € (equipment) and a yearly running cost of 2 000 €.

Action type: Development of individual skills

In order to achieve this, TRAIL will fund several activities focussing on the development of individual skills.

7 - mentoring programs (Master and Ph.D)
The LabEx will foster the setting up of the International Bio-Imaging Master of Bordeaux, starting September 2011, exclusively taught in English (in order to be internationally attractive and to prepare students to mobility, reading and working in English). Several of the teacher-researchers (professors, associate professors) of the IBIO Institute and the LabEx project participate to the master teaching in addition to their participation to several other master courses and teaching at the medical school. Based on annual calls for mentoring programs and interdisciplinary animation (such as developing skills for writing papers, teaching, publication strategy, setting up interdisciplinary seminars and workshops with international guests speakers, …) we will offer a broad and diversified range of learning activities. Another very important group is the PhD students.

The cost for one year of mentoring programme and interdisciplinary animation (6 sessions per year) is estimated to 45 840 € including,

Bonus for experienced mentors (equivalent to an half of a service statutory staff) : 35 000 €

Salary for a Ph.D student contributing to the programme (Bonus 1/5th of his/her service as planned in the French law) : 7 240 €

organisation fees: 3 600 €

8 - Master internships, that is supporting grants for 4-month internships in research laboratories or partners for transfer. Amounting to 500€ a month, these grants will help the student to acquire professional experience without being constrained by too severe financial restrictions.
8 such grants will be awarded each year. The overall cost for these internships has therefore been estimated at 20 000 € per year.

9 - Doctoral grants / Ph.D Student stipends
We wish to develop PhD student stipends through an annual call. This action will allow our own selection of PhD students that will include a pre-selection of the projects submitted and an oral examination of the pre-selected candidates. Finally, we will encourage the participation of the private

sector (industries, CRO, associations of patients, …) to teach in Masters or PhD degrees, to offer internships and to support financially the calls organized by the LabEx. Solutions of funding through the Foundation of Bordeaux University (a support structure of the LabEx) are offered to industries. Recently we obtained a 350.000 euros private funds from a radiological association for education in the field of Bio-Imaging. Our IBIO Institute and LabEx project has also raised funds with a recent engagement of AGFA company (see letter in annexes) with an initial investment of 240.000 euros dedicated to promote education and research.
The yearly cost of a Ph.D grant is **36 200 €** per year (2 600 euros/month).
Two Ph.D students will be recruited for a 3-year period every year from year 1 to year 8. A total of 14 Ph.D students are thus planned to be recruited for a 3-year period during the 10 years of the project for **total PhD Stipends Costs of 1 303 200 euros**

11 - Seminar on training objectives with invitation of Key note speakers, TRAIL will finance the organization of seminars to disseminate and discuss new training approaches developed by TRAIL Labex for the partners, collaborators and external audience (around 250 persons)

The average cost for one seminar is estimated to 10 000 € including

Organization costs subcontracted to external specialized company for **5 000 €**

Invitation of 2 Key note speakers for 4 days (two to three working days) ***5 000 €***
It is anticipated to organize **2 seminars per** year during 10 years

Equipment	Personnel cost statutory	Personnel costs (non statutory)	Missions	Sub-contracting (internal)	Sub-contracting (external)	Other running costs
6 - Video-vision conference equipment for remote teaching						
15 k€						**20 k€**
7 - mentoring programs (Master and Ph.D)						
	HR : 350 k€ 5 person (60 pm)	Ph.D: 72,4 k€ (2 person) 24 pm				**36 k€**
8 - Master internships						
		Intern : 200 k€ 80 interns (400 pm)				
9 - Doctoral grants / Ph.D Student stipends						
		Ph.D: 1 303 k€ (12 Ph.D)- 144 pm				
11 - Seminar on training objectives with invitation of key note speakers						
			100 k€			**100 k€**

*Details of the funding requested linked to the education project per type of cost: total cost for the programme ii estimated to about **2 M€** for the 10 year period. Person.month (pm)*

Exploitation of results.

TRAIL has defined one main goal to **provide a one-stop solution and showcase promoting relationships with industrial partners in the vicinity of Bordeaux as well as on a national and international level (e.g. with General Electric, Siemens, Philips)**
Although IBIO account with several industrial partnerships, we want to attract more industrial, large existing as well as small building-up companies to a reciprocal interest around imaging research and medically applied researches. We will develop a simple organization that will simplify the relationships with industrials and business offices. We will benefit from the know-how of industrial partners and they will benefit from integrated researches from bench to bedside with economic evaluations.

Structuring programme

3 - Business development capacity including,

A business developer to prospect opportunities for collaboration with medical industries (devices, contrast agent, pharmaceutical companies, …), to better understand the potential of development of our researches and teaching activities, and to alleviate researchers from administrative or commercial approaches. To organize the mutual understanding, we want to offer a one-stop industries service for the entire IBIO Institute and LabEx project, with respect of general rules for patents, transfer and valorisation in close coordination with the SATT of Bordeaux and other professional offices. We need to recruit a business developer (2011-2012) that will organize the one-stop service, will directly canvass industries and business offices, will display to the industries and private sector a good understanding of our researches and teaching activities. The initial salaries will come from LabEx funds to secure a non-tenure position for four years. After four years, in case of success, private funds should take over LabEx funds to finance these human resources.

The annual cost for the salary of the business developer (Economic School or Engineer + minimum five year experience preferably from private companies or industries) plus running costs for his/her activity: **is 100 000 € per year** (300 k€ for four years).

A fund dedicated to the financing of IPR management, provisioning:

- a lump sum of **5 000 k€** every year for an analysis by our TTO (Aquitaine Valo) of adequate protection for the knowledge generated by TRAIL;
- starting in 2016, a total fund for protecting IP generated out of the programme for a total of **250 000€.**

Equipment	Personnel cost statutory	Personnel costs (non statutory)	Missions	Sub-contracting (internal)	Sub-contracting (external)	Other running costs
3 - Business development capacity including,						
		1 full time over 4 years 288 k€ (48 pm)		**50 k€**	**250 k€**	**112 k€**

*Details of the funding requested linked to the exploitation of results per type of cost: total cost for the programme ii estimated to about **700 k€** for the 10 year period. Person.month (pm)*

governance (including links with socio-economics)

TRAIL has defined one main goal **to set up a strong governing organization and an internal animation, that fosters translational research in bio-imaging**

A significant part of the budget will be devoted to the structure itself over the first 4 years (2011-2015) a period at the end of which the partners will be evaluated by AERES, the French agency for Research and Education evaluation. The governing funds will be evaluated through three main indicators reflecting the quality of the coordination:

- the development of interdisciplinary partnerships in the LabEx between teams,
- the creation of a "Federation of Research CNRS – INSERM – CEA - University of Bordeaux - University Hospital - Cancer Hospital" between the partners.

After 4 years, it is expected to have additional incomes besides TRAIL funding (incomes generated by the project, reference institutions funding, etc.) and thus reach the financial sustainability at the end of the 10 year period.

Action type: Strengthening the life of the LabEx

13 - Permanent structure and running costs for the LabEx is thus including,

a. An Administrative Manager (also serving as LabEx Program director, financial manager, grant officer). The annual cost for the salary of the Administrative manager is **66 000 € per year** (462 k€ for 7 years).

b. An Animator (web site – seminars – socio-economic contacts – Public and Journals – LabEx Calls for project administrator - …). The annual cost for the salary of the animator is **48 000 € per year** (240 k€ for 5 years).

c. A secretary (attached to the Director of the LabEx and to the administrative manager). The annual cost for the salary of the animator is **48 000 € per year** (288 k€ for 6 years).

d. Running costs for the structure of three persons for a total of **50 000 € per year** (500 k€ for 10 years) and including the maintenance of Key Performance Indicators for the follow-up of activities and results of the LabEx.

e. Communication costs for promoting the LabEx and its activities for a total of **20 000 € per year** (200 k€ for 10 years) including a website and the production of dissemination supports such as flyers, movies, etc. These costs are subcontracted internally to the University of Bordeaux.

f. Scientific Board costs, for missions of members of the board coming each at least once a year and a total provisioned of **15 000 € per year** (150 k€ for 10 years).

Equipment	Personnel cost statutory	Personnel costs (non statutory)	Missions	Sub-contracting (internal)	Sub-contracting (external)	Other running costs
13 - Permanent structure and running costs for the LabEx is thus including,						
		3 full time persons 990 k€ (216 pm)	**150 k€**	**200 k€**		**500 k€**

*Details of the funding requested linked to the governance, including the link with socio-economics, per type of cost: total cost for the programme is estimated to about **1,8 M€** for the 10 year period. Person.month (pm)*

others resources

Financial participation of the associated research centres : the associated research centres of the LabEx will actively and financially participate in the project by covering for the "environment costs" involved by the personnel to be recruited in the research programs (PhD students, post-doc fellows, interns master).
These costs refer to the providing of office space, fluids, computers, access to the facilities (library, other platforms, subsidized catering, printing..).
Their total amount can be estimated using the budget key used by the CNRS in comparable cases, which is an additional 80% of the total personnel cost (salary and social charges).

Other funding expected for the LabEx project based on current capacity of actors to raise funds and existing commitments

The IBIO Institute promoting the LabEx TRAIL project has already received financial supports from:

1. National and Local Governments Contrat Plan Etat Région (CPER Grant): 12 000 000 euros for the 2009-2013 period.
    a. 12 000 000 euros are dedicated to a new 3500 m2 building which grand opening is schedule for 2013. This building will be located between the University Hospital and the University Segalen Bordeaux. In addition to this, IBIO will benefit from the Operation Campus programme that will contribute to the renovation of some buildings for research and education.
    b. 4 000 000 euros are dedicated to imaging devices: one PET/CT full time research which is operating since March 2010 (a 80.000 euros benefit this year re-invested on research); one Small animal MRI operating at 7T, opening May 2011

2. Several finances are coming from national, local and international calls. In the past five years the IBIO partners have raised for 27 500 000 euros (see section 4). Co-financing of LabEx TRAIL research projects will be encouraged in order to get LabEx TRAIL Grants (see section 6.1.1)

3. Industries: numerous contracts and supports with industries and private companies (see section 4)

4. Foundation University of Bordeaux
    a. We received a donation of 350 000 euros from a Radiological Private Association with the objective to promote education and research in imaging in link to the IBIO Institute
    b. The AGFA industrial partner is a trustee of the Foundation University of Bordeaux with the objective at promoting education and research in link to the IBIO Institute

Expected incomes generated by the TRAIL project
Through the recruitment of a Business developer, TRAIL is expecting to develop its transfer activity leading to incomes out of these activities flowing into the project after 4 years.
In addition, developing continuing education is also an important part of the LabEx strategy and should in the next years generate additional income for the LabEx activities.

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