National Infrastructure “France Life Imaging”

Activity Report for the Biomedical Imaging Advisory Board

November 2022

Introduction

France Life Imaging (FLI) is a large-scale infrastructure created in 2012 by the French Ministry of Research. It has been bringing together the main French centers of in vivo imaging research, structured in the form of 9 regional hubs, strongly connected by scientific and training networks. From a strategic point of view, FLI helped initiate a national policy for in vivo imaging equipments making them available to all researchers in most domains of Science in France. It also enabled, through 5 dedicated networks (4 thematic and 1 on training), an exchange of know-how and skills between platforms from all over France. Finally, FLI accompanied the development of a secure infrastructure for analysis and management of the data generated on the in vivo imaging platforms.

FLI was renewed in 2019 after evaluation by an international jury. The validated project aimed to continue the structuring effort and to extend the infrastructure to new imaging platforms. This new project also proposed to transform the original « Scientific Advisory Board » into a « Biomedical Imaging Advisory Board » (BIAB). The term Scientific in the SAB of the initial project was at the origin of much confusion. The coordination of FLI cannot have any responsibility on the scientific value of the work achieved on these platforms. Each platform must be supported by at least a research team, evaluated in the French system by Hcéres, universities and NRO. Thus, the name of Scientific Advisory Board is improper to evaluate the infrastructure and we preferred the term of « Biomedical imaging Advisory Board » (BIAB). In that sense, the scientific results (publications and patents) obtained on the FLI Platforms are certainly an element but the evaluation will be carried upon the policy of the infrastructure rather than on these results.

It is in this spirit that the FLI Steering Committee submits this activity report to the BIAB. This report precedes a visit by the BIAB scheduled for December 9, 2022. FLI would like to warmly thank the 4 BIAB members for accepting this evaluation and advisory work. Without prejudging the analysis that BIAB will make of this document and of the oral presentations on December 9, the FLI steering committee would be grateful if BIAB members could share their view on the perspectives proposed by our four thematic networks of expertise, on the training strategy, on the way of encouraging the integration of the platforms into FLI, on the enlargement of the infrastructure, on the strategy of perpetuating FLI and on what FLI could possibly expect from integrating into European infrastructures.

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Contents

1. Overall presentation of the Infrastructure

1.1 Missions and objectives

France Life Imaging - FLI - is a large-scale infrastructure bringing together the French medical imaging research platforms. These platforms include state-of-the-art preclinical and clinical imaging systems, mainly magnetic resonance imaging (MRI), radioisotope imaging (including positron emission tomography), computed tomography (CT), ultrasound and magnetoencephalography (MEG). Launched in 2012, FLI has three main missions:

1. To coordinate the French medical imaging research platforms in order to offer a large access to state-of-the art imaging devices to life science research communities,
2. To strengthen the scientific expertise of the platforms,
3. To provide the research labs with solutions for image analysis and management.

To carry out these missions, the Ministry of Research granted the infrastructure with 37 M€ for the 2012-2019 period and 6 M€ for the 2020-2024 period (FLI was renewed after evaluation by an international jury in 2019). These grants made it possible to:

- Set up a national structuration of imaging platforms in the form of 9 regional hubs[a] integrating 39 platforms nationwide (Fig. 1 left),
- Finance equipment acquisition/upgrade to improve the national offer in imaging (22 M€ over 2013-2019),
- Set up an ambitious program of exchange of expertise between platforms in 4 core scientific domains: molecular imaging agents, instrumentation and innovative technologies, interventional imaging, and multimodal image analysis (3.6 M€ allocated for 2012-2024, Fig. 1 middle),
- Set up a training program for students and researchers (0.7 M€ allocated for 2012-2024),
- Implement an infrastructure for Image Analysis and Management (IAM hub) and for the development of open science (4.2 M€ allocated for 2012-2024, Fig. 1 right).

These structuring actions have enabled the research communities to develop innovations in imaging, based on new collaborations between platforms. At the same time, the platforms have opened up to the biology and health research communities and to industry.

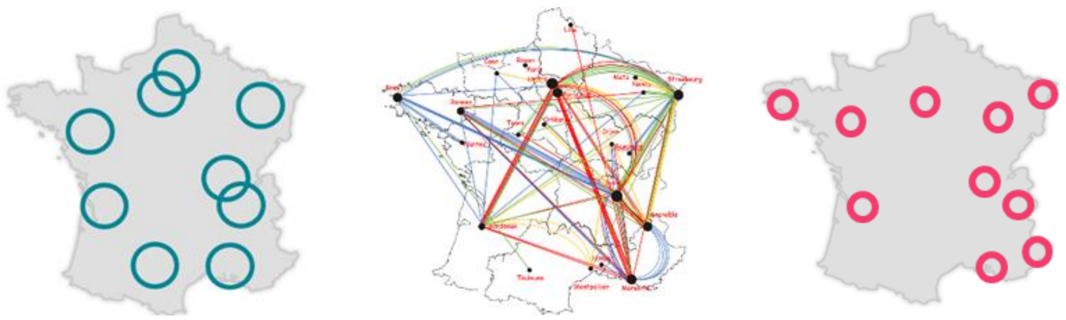

Fig. 1. Regional hubs coordinated by FLI (left) – Exchanges of expertise between platforms funded by FLI (middle) – Laboratories involved in the Image Analysis & Managment (IAM) hub (right)

1.2 Governance

FLI is a consortium of 16 academic partners coordinated by CEA: 4 NRO and 12 Universities. FLI has 3 main bodies of governance (Fig. 2):

[a] 6 hubs created in 2012, 3 new hubs created in 2020

- a national steering committee with representatives of the hubs, the 4 networks of expertise and the network of training as well as the national coordinator and executive coordinator, that meets every month since 2011. It addresses the strategic orientations of the infrastructure, monitors the performance of the infrastructure and the actions of the networks (expertise and training), and sets-up the communication strategy,
- a board of institutions including representatives of the 16 national research organisms and universities that meets once a year. It validates the propositions of the steering committee and approves the budget,
- a biomedical imaging advisory board (BIAB) advising the steering committee on its strategy, composed of 4 members:
  - Jacques Bittoun, former President of Paris-Sud University,
  - Claire Corot, Truffle Capital, former Director of the Research Department at Guerbet,
  - Jolanta Kunikowska, Nuclear Medicine Department, Medical University Warsaw/Poland, President of the European Association of Nuclear Medicine (EANM),
  - Oliver Speck, Dept. Biomedical Magnetic Resonance, Faculty of Natural Sciences / Institute for Physics, Otto von Guericke University Magdeburg.

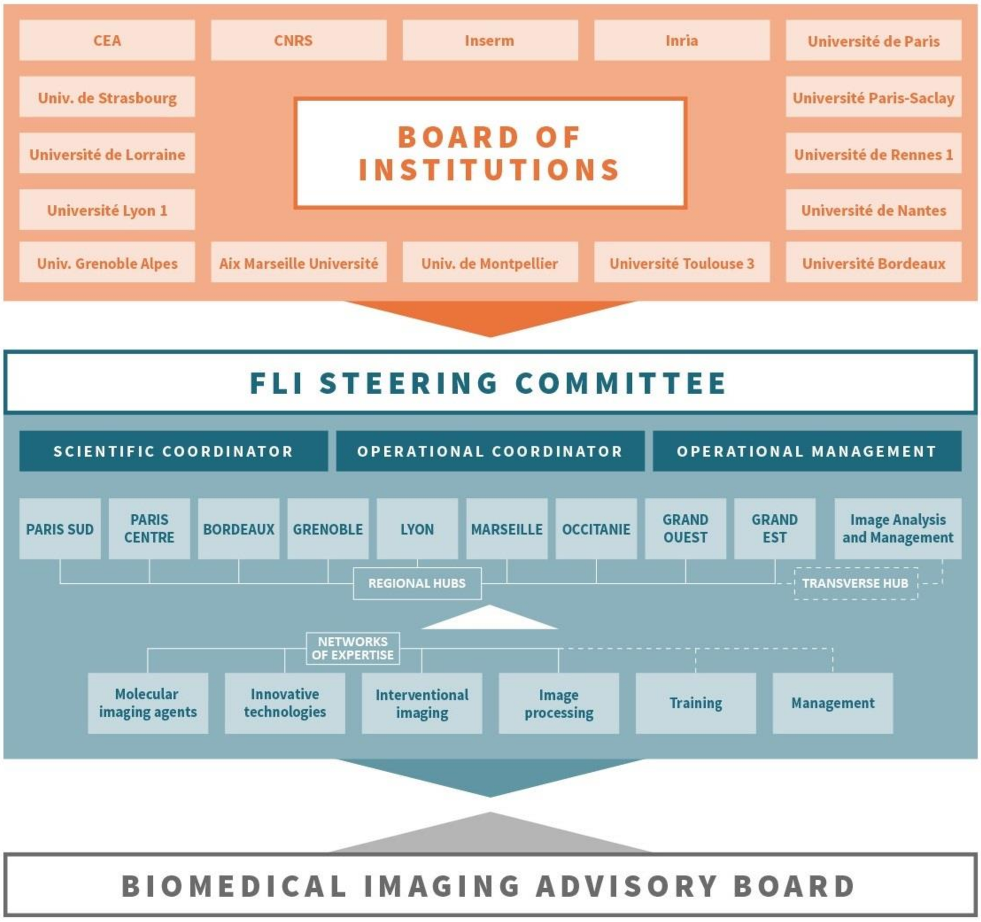

Fig. 2 FLI's governance

A steering committee is also implemented at the level of each hub, network of expertise and training. Guidelines specifying the basic animation of the hubs, including meetings every quarter at least were proposed to the regional and IAM hubs, and to the networks of expertise and training.

Vincent Lebon is the coordinator of FLI since 2019, Régine Trebossen is the executive coordinator since 2012. They are assisted by two staff for the management of the “Exchanges of Expertise” program (see section 3) and the management of the Training Network actions (see section 4).

1.3 Recent developments

As mentioned above, FLI was renewed in 2019 until 2024. Since 2019, FLI has been continuing its actions of structuring and scientific networking. This sustained work has been complemented by the following recent developments:

- the inclusion of 3 new regional hubs (Occitanie, Grand-Ouest, Grand-Est) in addition to the 6 original ones and the corresponding inclusion of 7 new universities to original consortium,
- the drafting of a national prospective document for the acquisition of imaging equipment,
- the application to call for proposals for equipment funding.

2. Structuring platforms nationwide: the 9 regional hubs

2.1 Description

The first objective of the FLI infrastructure was to structure the French medical imaging research communities. To do this, the territory was meshed into 6 regional hubs in 2012, then extended to 9 hubs in 2020 (Fig. 1 left). This provides almost complete coverage of the territory, bringing together 39 research platforms and a total of 159 in vivo imaging systems.

The 6 original regional hubs are: Hub Marseille (5 platforms, coordinator Monique Bernard), Hub Bordeaux (3 platforms, coordinator Vincent Doucet), Hub Grenoble (6 platforms, coordinator Daniel Fagret), Hub Lyon (2 platforms, coordinator Philippe Douek), Hub Paris-Sud (4 platforms, coordinator Sébastien Jan), Hub Paris-Centre (6 platforms, coordinator Philippe Garteiser). The 3 recently created hubs are: Hub Occitan (5 platforms, coordinator Isabelle Berry), Hub Grand-Ouest (3 platforms, coordinator Jean-Christophe Ferré), Hub Grand-Est (5 platforms, coordinator Jacques Felblinger).

2.2 Governance

Each hub relies on a local steering committee composed of the researchers and/or engineers responsible of all the platforms of the hub and of all the scientific units supporting them. The members of the local steering committee appoint by consensus a coordinator who will represent the hub in the national steering committee. In order to help structuring the regional hubs, a specific funding has been dedicated to the recruitment of a project manager for each hub for the 2020-2024 period. Recruitments have been performed except for two hubs for which they are still pending.

The steering committees of the regional hubs meet regularly (at least every quarter). Through these meetings, the managers of all French platforms are directly involved in the functioning of FLI: sharing of infrastructure information, dissemination of the “Exchange of Expertise” calls for proposal (see section 3), dissemination of FLI training offer (see section 4), dissemination of FLI-IAM offer (see section 5), contribution to FLI's prospective documents (see section 6.1) ...

Since 2020, FLI has made efforts to integrate the 3 new hubs into the existing network in several ways:

- Organization of meetings of the national steering committee in regional hubs associated with the visit of regional platforms twice a year,
- Organization of meetings bringing together all hub project managers to share best practices,
- Organization by regional hubs of FLI annual meetings to allow the beneficiaries of the “Exchange of Expertise” grants to share their projects and their results.

It is important to note the remarkable involvement of the hub coordinators who play an essential role in the functioning of FLI. However, local constraints vary from one region to another (geographical distance between platforms, lack of a history of collaboration, etc.), so that the dynamics of local structuring remain variable, particularly in the hubs that have been created recently. FLI will have to continue its efforts and ensure that all hubs reach the same degree of integration in the forthcoming years.

3. Developing scientific expertise: the 4 Networks of Expertise

Once the imaging platforms were organized into a network of hubs, FLI was able to implement scientific animation of the platforms. The objective of this animation program is to strengthen the scientific expertise of the teams operating the platforms and to make sure expertise is maintained at the highest level. To this end, networks of expertise (NE) have been set up in 4 fields covering in vivo imaging research: molecular imaging agents (NE1), instrumentation and innovative technologies (NE2), interventional imaging (NE3), and multimodal image analysis (NE4).

Each Network of Expertise relies on a steering committee bringing together experts and representatives of all hubs. The 4 networks of expertise have renewed and enlarged their steering committees in 2019 in order to account for emerging research themes in medical imaging.

Each NE animates large research communities by supporting exchange of expertise between distant platforms. Calls for proposal « Exchange of Expertise » are opened by each NE on a regular basis since 2012. The calls offer up to 30,000 € starting grants to 2 distant research teams submitting a collaborative project aiming at sharing a particular expertise. In order to include laboratories that do not belong to FLI, these calls are open to all French research laboratories. Since 2012, 141 starting grants have been awarded to foster collaborations and exchanges of know-hows (including 52 grants awarded since 2020), for a total of 2 576 000 €. It is very likely that these collaborations would not have been possible without FLI.

3.1 Network of Expertise 1: Molecular Imaging Agents

Scientific scope of the Network

The production of appropriate imaging agents has been identified as a major obstacle to medical imaging research. Indeed, although some laboratories have the capacity to generate these agents for their own investigations, they are not able to supply other centers. Therefore, the objective of this work package is to provide a framework for the production of imaging agents for which there is no commercial supply and to generate new imaging probes or contrast agents for in vivo biomedical research and clinical applications (e.g. optical agents, radionuclides, magnetic resonance agents, etc.)

The Network of Expertise 1 (NE1) intends to stimulate interdisciplinarity in collaborative projects in medical imaging and to accelerate the design, fabrication and eventual clinical use of new molecular imaging agents with greater sensitivity, selectivity and minimal toxicity. NE1 is thus organized in 4 domains:

- NE1.1 “Modular targeting platform for imaging”: development of synthetic macromolecules & labeling techniques.
- NE1.2 “Development of probes and contrast agents”: introduction of short-lived radionuclides, optimization of the binding properties of chelating agents (for MRI, Optical, SPECT and PET applications), optimization of agents used in MRI and optical imaging, development of innovative technologies including clickable, intelligent and multimodal probes.
- NE1.3 “Nanoparticles for imaging”: development of nanoparticles for multimodal imaging, development of multifunctional nanoparticles with high specificity and detectable in imaging
- NE1.4 “Proof of concept, clinical applications, translational research”: scale up process: from chemistry lab to production, proof of concept and preclinical and clinical trials

Laboratories associated to the Network

NE1 brings together ~30 research laboratories which are nationally labelled either by CNRS (institute of chemistry and institute of biology) or INSERM. They are spread over most of the French region and universities. Their research activities cover the large spectrum of organic chemistry and chemistry for medical application, with a focus on the development of synthetic macromolecules and radiolabeling methods of these molecules, the development of probes and contrast agents, nanoparticles for imaging purposes.

Starting grants "NE1 - Exchange of Expertise"

Since the creation of FLI, 25 starting grants "Exchange of Expertise" have been awarded by NE1, including 13 grants awarded since 2020[b]. Average grant amount was ~27,000 €. These grants were allocated to 33 different labs, for a total amount of 675,225 €. Many of the grants involved laboratories located outside the hubs (Orléans, Tours, Rouen, Caen, Dijon, Reims). Many of the funded projects were translational research projects including in vivo small animal proof of concept.

Perspectives

In the field of imaging agents, the main trends are related to:

- the development of novel radiotracers for PET imaging,
- the development of bimodal imaging agents driven by hybrid imaging coupling acoustics.

In terms of medical applications, the majority of projects are focused on oncology, but there is a growing demand for inflammatory diseases.

3.2 Network of Expertise 2: Instrumentation & Technological Innovations

Scientific scope of the Network

Medical imaging has held an established place in the clinical armamentarium for nearly 40 years. Instrumental and technological developments continue to be the primary driving force in the quest to better assess the presence and severity of disease and the response to treatment. More pertinent clinical and preclinical information should be established with quantitative parameters (biomarkers).

The Network of Expertise 2 (NE2) aims to develop specific approaches and promote breakthroughs in each medical imaging modality: higher magnetic fields and optimized low-field technology in MRI; 3D, ultrafast, ultrahigh resolution and targeted agent detection in US imaging; dedicated systems and innovative concepts in ionizing radiation (X- or gamma-ray) imaging; wider access to preclinical and clinical studies in optical imaging. In addition to these individual challenges, combining two or more imaging modalities open radically new perspectives for diagnosis and therapy with increased sensitivity and specificity. Modalities can interact either at the physical signal level (hybrid or multiwave imaging), or at the processing level to provide multimodal imaging biomarkers.

Laboratories associated to the Network

At least 83-labeled French academic units develop original researches within NE2 objectives, including 7 in Bordeaux, 9 in Grenoble, 7 in Lyon, 9 in Marseille, 15 in Paris Centre, 9 in Paris Sud, 6 in Grand Est, 6 in Occitan, 5 in Grand Ouest, and 8 outside hub perimeters (Orléans, Tours, Caen, Poitiers, Clermont-Ferrand, Lille, Dijon). Among these, 31 developed active collaborations in the frame of NE2 with main expertise in MRI (66 %), PET (10 %), US (10 %), Optical imaging (10 %) and MEG (5 %).

Starting grants "NE2 - Exchange of Expertise"

Since the creation of FLI, 39 starting grants "Exchange of Expertise" have been awarded by NE2, including 16 grants awarded since 2020[c]. Average grant amount was ~16,000 €. These grants were allocated to 31 different labs, for a total amount of 629,000 €. Among currently running projects, each partnership, excepted one, involves at least 2 hubs simultaneously, 4 projects involve 3 hubs and 1 project 4 hubs; 2 projects are shared with NE1 or NE4. Thirteen (13) projects are focused on MRI, 2 on US, 1 on MEG, 1 on TEP, 1 on acousto-optics and 1 mixed US-MR. Four (4) projects are mainly concerned by facing protocol robustness and safety issues in ultra|high-field MRI, 6 by developing MRI biomarkers (SEP, lipidic content, brain oxygenation, cardiac-transplant viability, high-resolution multiparametric imaging, free-face IRMf), 3 by intracardiac-deployable or brain-implantable miniature MR coils, 1 by accommodating awake non-human primates in a ultra-high-resolution PET system and 5 by disruptive concepts: in-vivo acousto-optics, implantable wireless US-transducer network, anisotropic/non-linear MR or US elastography, MEG with laser-pumped magnetometers.

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[b] No grant was awarded in 2020 due to the COVID-19 crisis ; the 13 grants were awarded in 2021-2022

[c] Only 1 grant was awarded in 2020-2021 due to the COVID-19 crisis; 15 grants were awarded in 2022

Perspectives

NE2 will keep a scientific and technologic watch on the following topics:

- In **MRI**, developing multiparametric biomarkers calls for accurate and accelerated protocols involving innovative approaches such as compressed sensing and finger printing. This is particularly constraining at high magnetic fields, hindered by long-T1 and RF-deposition issues, or at low fields facing sensitivity thresholds. Patient accessibility should be a major focus in MRI. To improve specificity, imaging unsensitive nuclei is another challenge that is still to be handled, either by calling to ultra-high fields, or with long-lived hyperpolarization approaches accessible even at low-fields.
- In **US**, French ground-breaking works should be further pushed: US neurostimulation, complex blood flow mapping, super-resolution imaging, theranostics with feedback loops, quantitative assessment of tissue microstructure and shear-wave propagation. Driving innovations will include the refinement of ultrarapid architectures, new developments of probes and sequences optimized for focusing power, of multi-frequency and 3D capacities, and integrated “intelligent” software in devices.
- In **ionizing radiation imaging**, new technologies are emerging with Rx rays, such as phase-sensitive, spectral or Compton scattering scanners, allowing to better assess soft tissues and contrast agents. Related issues are with counting detector designs and dose considerations. With gamma-rays, full whole-body TEP cameras can dramatically improve sensitivity and pharmaco-dynamics assessments, while reducingde the time resolution of detectors can ultimately give access to real-time 3D resolution. Improved spatial resolution and sensitivity are also becoming accessible with new detector technologies, where smart detectors with integrated real-time IA processing might be a key feature.
- **Optical imaging** constitutes a well-adapted modality for functional imaging in small animals, able to reach picomolar detection ranges, which can be nicely combined with therapeutic agents but suffers from quantification, dye-toxicity and wave penetration issues. The keys are to discover optically active nanoparticles, combined with multi-spectral diffusion optical tomographs to detect several dyes in real-time. Miniaturizing devices is also required for endoscopic or peroperative imaging. The optical imaging technology for small animal is well advancing, and photoacoustics open a way towards clinical imaging at few-millimeter resolution. But quantification remains a major bottleneck to overcome.
- **Hybrid/multiwave imaging** is an expanding research playground with various degrees of maturation: PET-MR scanners, routinely available for preclinical and clinical examinations; US, MRI and optical elastography; photo-acoustic, acousto-optic and opto-MRI; hybrid MRI-PET-US doppler… Beyond fascinating scientific challenges and perspectives, these new imaging systems must be investigated by pluridisciplinary teams to evaluate their actual added values for patient care or for drug development.
- **Imaging biomarkers** for a particular disease rely on carefully established parameters and standardized protocols, validated by multicentric cohort studies with different brands of scanners/cameras to prevent potential biases. Having a structured community such as in FLI, in conjunction with networking initiatives such as REMI, Appning and FORCE Imaging, gives a real potential to take the challenge. Efficient development of biomarkers in FLI also needs interactions with RE4 and IAM, as well as with RE1 to push functional imaging at molecular-interaction levels.

3.3 Network of Expertise 3: Image Guided Interventional Radiology

Scientific scope of the Network

Medical (clinical, preclinical) and interventional imaging is a major issue in public health to better understand, detect, diagnose, predict and cure various pathologies (neurological, oncological, cardiological, vascular, etc.). It should help doctors in the interpretation and analysis of many images of different modalities for the same patient for applications in diagnosis (preoperative) and interventional imaging (intraoperative). Interventional procedures controlled by imagery are in full expansion and could overtake surgical procedures in the next 10 years. This increase is closely linked to technological progress in disciplinary fields ranging from imaging systems and image processing to intervention devices and robotics systems.

The purpose of interventional radiology is to treat various pathologies (tumors, vascular lesions, etc.) using minimally invasive techniques guided by intraoperative imaging, by accessing them through natural pathways, blood vessels or percutaneous route. Interventional imaging is characterized by the development of intraoperative imaging techniques (in the broad sense) to assist medical-surgical procedures in order to improve the quality of care and shorten the length of hospitalization.

This field is evolving rapidly and is at the crossroads between several medical specialties: surgery, radiology, endoscopy, radiotherapy, cardio/neurology, etc.

Laboratories associated to the Network

41 research laboratories and 10 hospitals have benefited from "NE3 - Exchange of Expertise" grants. Recipients are located either within a regional hub (33) or outside (8), demonstrating the openness of the network's grant allocation system and its broadly inclusive nature. The granted research laboratories are under the supervision of the CNRS, Inserm, CEA and universities (Univ. of Strasbourg, Univ Grenoble-Alpes, Aix Marseille Université, Univ Claude Bernard Lyon1, Université de Tours, Univ. de Toulouse, Université de Rennes).

Starting grants "NE3 - Exchange of Expertise"

Since the creation of FLI, 42 starting grants "Exchange of Expertise" have been awarded by NE3[d], including 8 grants awarded since 2020[e]. Average grant amount was ~13,000 €. These grants were allocated to 24 different labs, for a total amount of 552,000 €. The leverage effect of this support is very important and has enabled the emergence of numerous national and international research projects.

Perspectives

Main advances expected in the next few years in the field of interventional imaging:

- **Navigation and augmented reality**

Navigation and augmented reality systems can only be used safely in a clinical setting if new advanced image processing methods are offered. For example, multimodal, robust, accurate and real-time registration and segmentation methods are mandatory. This constitutes the first work perspective for the next few years.

A second perspective is the optimization and the monitoring of the dose received by the patient and the medical staff during navigation that use X-ray systems. Due to the growth of such intervention real-time computational dose calculation at the organ level must be implemented in the operating room.

Whether for image processing or dose calculation, artificial intelligence will play a key role to achieve our objectives.

- **Imaging systems and interventional robotic systems**

The clinician should be able to focus on tasks of clinical importance while the robot assists by performing tasks in a semi-automated manner with simultaneous command sharing.

An example is the compensation of physiological movements: the clinician performs movements relative to the tissue while the robot compensates for the physiological movements, both being performed simultaneously. We can also note in this context all the "prohibited zone" assistance modes: the robot prevents movements in a certain direction, or prevents entering a dangerous zone, while the surgeon is free to navigate elsewhere. The command is shared and the robot acts semi-automatically (i.e. supervised by the clinician). Again, there are synergies with the field of navigation

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[d] 42 grants awarded for 55 submitted projects

[e] No grant was awarded in 2020 due to the COVID-19 crisis; the 8 grants were awarded in 2021-2022

and augmented reality because workflow recognition or per/pre-op registration can give an indication of the position of prohibited areas, for example.

- **Medical interventions guided by MRI**

Technical and scientific advances should make it possible to promote minimally invasive precision surgery augmented by artificial intelligence, virtual reality and robotics and to integrate it into new care pathways using e-health tools and favoring early diagnosis, outpatient procedures and advanced patient monitoring. The rise of innovative image-guided therapies will ensure targeted and personalized patient care.

- **Ultrasound-based therapies (HIFU and targeted delivery)**

Therapeutic (US) ultrasound is constantly evolving. To improve patient care and offer new applications, “personalized” therapies - focal or conformal - should make it possible to better target pathological sites while sparing healthy regions. However, these therapies remain very complex to implement, as they require advanced control of US emission and “US/tissue” biophysical interactions. To guide these new procedures, US bimodality (imaging/therapy) and multimodal imaging (e.g. US, MRI, modeling, fusion) are promising. Biomedical ultrasound could benefit even more in the future from innovative solutions from a wide variety of fields (e.g. medical imaging, digital modelling, instrumentation, microelectronics, robotics). Existing and future synergies with other areas are therefore particularly natural.

3.4 Network of Expertise 4: Multimodal Image Analysis

Scientific scope of the Network

Multimodal imaging plays an increasingly important role in the diagnostic and therapeutic follow-up phases. Today, it uses nuclear imaging modalities (PET, SPECT) as well as CT and MRI imaging. This use is made possible in part by image processing. Firstly, it ensures both quantitative and qualitative accuracy of the acquired data and consequently of the different parameters extracted from the reconstructed images. Secondly, image processing allows the subsequent exploitation of the parameters derived from the images and facilitates the development of anatomical and physiological models necessary for the understanding of pathological mechanisms. Finally, the combination of these models and multimodal images associated with biological data makes it possible to establish a unique signature for each patient and thus facilitate the implementation of personalised medicine.

Laboratories associated to the Network

NE4 gathers 24 research laboratories with strong expertise in medical image analysis located in most of the French regions. Supervising institutions of these labs include CNRS, INSERM, INRIA, IPP, Institut Mines-Telecom, INSA, Univ. of Rennes, Univ. of Strasbourg, Univ. Paris-Saclay, Univ. Lyon 1, Univ. Saint-Etienne, Univ. Bretagne Occidentale, Univ. Grenoble Alpes and Aix-Marseille Univ.

Starting grants “NE4 - Exchange of Expertise”

Since the creation of FLI, 44 starting grants “Exchange of Expertise” have been awarded by NE4, including 16 grants awarded since 2020[f]. Average grant amount was ~16,000 €. These grants were allocated to 41 different labs, for a total amount of 720,000 €. One specificity of the projects funded by NE4 is that half of them gather three different laboratories or more. They cover multimodal image analysis, image reconstruction for PET, PET-MR, MEG and Single Photon Counting Scanner, quantitative methods for MRI, AI.

Perspectives

Co-design" approaches in which the imaging, detection or measurement device is closely associated with the algorithms used to process the data are gaining ground. The design of these new instruments is based on an approach of simultaneous modelling and optimisation of the parameters of the instrument and the digital processing associated with the targeted application. This joint "co-design"

[f] No grant was awarded in 2020 due to the COVID-19 crisis; the 16 grants were awarded in 2021-2022

allows the development of new instruments, for which the instrument and the processing are inseparable. In addition, in recent years, a number of hardware innovations have been introduced for anatomical and functional imaging modalities, with the aim of improving the quantitative accuracy and quality of reconstructed images. The development of new detectors allows the measurement of additional information that will be incorporated into future generations of clinical multimodal imaging systems. Examples include the measurement of interaction depth in PET, or the use of semiconductor-based detectors for single-photon emission computed tomography (SPECT) and X-ray spectral imaging in CT. Reconstruction methods that would allow all this new information to be taken into account, as well as the correction of all causes of degradation, could provide images of unparalleled quality.

Further characterisation of a physiological process, by combining the information provided by multimodal images, has the potential to go further and provide a better understanding of the mechanisms involved, and ultimately to improve patient care. However, this combination is not obvious as the different modalities have different characteristics in terms of sensitivity, spatial/temporal resolution, and noise properties (types and intensities). In addition, other parameters are available, notably clinical, phenotypic and genotypic data, results of biological analyses (biopsies, markers, etc.) and must be taken into account. The methodological developments envisaged in this area will combine developments: (i). dedicated to the analysis (automatic segmentation, extraction of quantitative multiparametric signatures) of multimodal PET/CT/MRI images, (ii). in terms of machine learning (feature selection, classification) for an appropriate combination of multi-source information within the framework of the development of predictive and prognostic models, accompanied by validation studies on cohorts.

Finally, in all the above perspectives mentioned the role of deep learning (DL) needs to be established in the clinical domain. There has been over the past 5 years a significant body of scientific work clearly demonstrating the enormous potential of DL in all areas of medical imaging (detector design and conception, image reconstruction, image processing, predictive and prognostic modelling). An increasing number of medical imaging devices are actually using DL at one or multiple stages of their operation but the application of these techniques in every day clinical practice rests today limited, an aspect that represents a challenge to overcome for the years to come. Multi-center trials, data harmonization, robustness and reproducibility, interpretability, and real clinical impact are some of the aspects that need to be assessed and evaluated in order to provide the necessary evidence of clinical impact and eventually help in the widespread adoption of these techniques.

3.5 Leverage effect of the "Exchange of Expertise" starting grants

Several starting grants enabled partners to apply successfully to national or international funding agencies, demonstrating the leverage effect of FLI exchanges of expertise.

Since 2013, fifteen starting grants led to a total extra-funding of 15 M€ either by the French Research Agency, foundations or H2020. Examples of extra-funding include the following projects:

- IMOP (Interoperative Multimodal Optical Probe, 250 k€) awarded by the *Plan Cancer*,
- ARMONI (single pixel imaging methods, 280 k€) awarded by an ANR JCJC,
- OptimiX (Optimization of the radiation dose for X-ray guided procedures, 497 k€) awarded by ANR PRC,
- GlyoSpy (Photoswitchable Nanoparticles for High-Contrast Photoacoustic Microscopy to Image Inflammation, 588 k€) awarded by ANR,
- ROBOT (Robotics and Optical coherence tomography for optical BiOpsy in the digestive Tract, 452 k€),
- M-CUBE (3.9 M€) awarded by FET-OPEN,
- QuantSURG (1.6 M€) awarded by ERC,
- MRgHIFU (MRI-guided high-intensity focused ultrasound, 628 k€) awarded by ANR,
- SURGEONAID (Transforming brain surgery by advancing functional-guided neuronavigational imaging, 4.4 M€) awarded by Europe EIC Pathfinder,

- NIFUS (Non-invasive focused ultrasound surgery of breast adenocarcinomas, 331 k€) awarded by INCa.

In another domain, one of the exchanges of expertise granted by FLI in 2020, concerning the testing of new sensors for MEG, has contributed to the creation of Mag4Health - a startup supported by the CEA - that will commercialize the tested sensors.

Finally, the work carried out within the framework of two exchanges of expertise has led to the implementation of an open-source software platform for 4D image reconstruction used by more than 200 users (https://castor-project.org/).

3.6 Additional Networks

In addition to the 4 NE, three networks of skills were created: the REMI network (Multicentric Mutual Aid Network in MRI, https://www.francelifeimaging.fr/reseaux-connexes/remi/), the 7T MRI network and the Small Animal Imaging Network (SAIN).

REMI network was launched thanks to the initiative of three representatives of Paris Centre, Marseille, and Grenoble hubs and two representatives from Rennes and Nancy. The aim of the network is to share skills and specific 'tips and tricks' and provide mutual assistance to minimize artefacts in MRI and optimize image quality for the clinical research in research centers and in a hospital environment. Supported by FLI, the network gathers more than 60 MRI platforms in France and organized several technical, methodological and organizational working groups.

A specific network devoted to mutual assistance of the MRI physicists working with 7T scanners for humans was also supported by FLI. Such expensive systems also require support from a team of physicists to overcome the impact of artefacts reducing image quality and interpretation.

FLI also supported the creation of a network dedicated to small animal imaging (SAIN), which gathers at the national level scientists involved in small animal imaging and organizes advanced seminars in small animal imaging.

4. Developing training in medical imaging: the Training Network

The Training Network is coordinated by Albertine Dubois and relies on a steering committee gathering representatives of the 9 regional hubs and the 4 NE.
The objective of the Training Network is to ensure a high level of education in the field of biomedical imaging within, throughout and across the FLI consortium, for both students and professionals. The main achievements since 2012 () are both:

- **<u>The improvement of the training and professional integration of students through:</u>**
    - the **allocation of 790 (scholarships per year for students and post-doc** to take part in French and international workshops, trainings or congresses (**274 since 2019)**
    - the financial support to several French master programs for the implementation of **9 state-of-the-art lab work sessions on FLI core-facilities** for a wide range of biomedical imaging modalities (MRI, ultrasound, nuclear medicine) allowing the **training of 634 students (418 since 2019)**
    - the implementation of the French Imaging Network of Young Scientists (FINYS) aiming at increasing the employability and visibility of the students and young post-doc among academic and industrial partners
    - the communication actions toward the master degrees and doctoral school coordinators.

- **<u>The coordination, support and update of the continuing professional development (CPD) actions for the staff and users of the core-facilities through:</u>**
    - the identification of the training needs of the academic and industrial scientific community

- the support to ongoing nationwide training actions and **the allocation of support grants for 348 professionals to attend these trainings (83 since 2019)**
- the organization of training courses in MRI safety for healthcare workers, small animal ultrasound imaging, the use of CASToR platform (Customizable and Advance Software for Tomographic emission Recontruction, developed by the Network of Expertise 4 - Multimodal image analysis) for which certificates are provided. All these training courses have been developed in collaboration with professionals from FLI lab and research platforms
- the promotion and recognition of staff mobility and exchange within the FLI consortium leading to the mobility of several lab engineers and technicians each year.

Note that, due to the cancellation of most training actions, conferences, workshops and congresses in 2020 (COVID-19 crisis), FLI Training Network was not able to allocate any financial support that year.

5. Offering image analysis and management tools to research communities: FLI-IAM

5.1 Objectives

The goal of the Image Analysis and Management (FLI-IAM) hub was to develop a *secure infrastructure* for **the storage** of the imaging data and associated meta-data (acquisition conditions, additional recordings, …) generated on the various *in vivo* imaging platforms forming the FLI infrastructure; and for the **definition and execution of efficient algorithms** for processing the images *corpus*. The need for such a specific infrastructure is reinforced by the recent introduction of machine learning techniques (AI named) that require the processing of large mass of imaging data (annotated or not) with dedicated computational hardware. Our ultimate objective is to facilitate the opportunities linked to **digital commons** i.e., to increase **the visibility,** via a web portal, of the imaging data produced on the FLI platforms, and to **diffuse** largely the software developed by the associated methodological research teams (see Networks of expertise 2 and 4). By providing such an accessible platform, we offer a central support to multi-center clinical and preclinical studies, and **promote controlled data sharing and data reuse** for *in vivo* imaging (**open science** movement).

During a first stage (2014-2019), a demonstrator (***R&D***) was developed that supported preclinical multi-center studies[1], different international challenges for software performance evaluation (MSSEG-I 2016[2], MSSEG-II 2021, and Pet-Tumor 2016[3]) and the sharing of preclinical data[4] or clinical data, under open but controlled conditions[5,6,7]. The demonstrator was based on two major robust components Shanoir[8] and VIP[9] (see Figure 1) already used in different large projects (for instance management of the French national Multiple Sclerosis project, OFSEP, 30000 patients expected). The ***R&D*** team (Shanoir and VIP project managers: M. Kain and S. Pop respectively) benefited from a financial support 1.74 M€ and involved 486 man-month.

5.2 Industrial operation

During the second stage (2020-23) a partnership is developed with GME, an association of three French industrials[g]. The GME's roles are 1) to maintain a secured and heath data certified cloud environment, with an access to virtual machines for intensive computations; 2) to integrate, in continuous releases, the innovative developments provided by the ***R&D*** team; 3) to promote, via marketing and commercial actions, the platform to public and private users; 4) to manage the platform (user account creation, bugs correction, user training, quotations, …); and 5) to propose an economically viable business model. The lessons learned from this industrial partnership are plural. First, the platform corresponds to real needs: many clients, in majority from public institutes (laboratories or hospitals) are interested in the offer. Second, the commonly defined price list is adapted: more than ten current contract

[g] Digital&Ethics, Sys&Com and Euris Cloud Santé

signatures. Third, ***R&D*** actions are still required to fulfill the evolution users' needs. Indeed, the availability of such a platform generates new needs and new services. The amount of 1.2 M€ was dedicated to this industrial operation. Three engineers (3 years) are financially supported by FLI for the ***R&D*** action.

5.3 Perspectives

Clearly, based on our expertise in *in vivo* imaging management and processing, obtained thanks to the FLI community of engineers and scientists, our objective is that **FLI-IAM*** becomes a central French and European actor for the management of **FAIR** (Findable, Accessible, Interoperable and Reusable) imaging data and for the promotion of **Open science** in a controlled way ("as open as possible, as restricted as necessary"). Our main future actions will be to reinforce the **FLI-IAM interoperability** with other national and European Biology & Health infrastructures (*in vitro* imaging and genetics), for multi-scale and multi-modality clinical and preclinical studies. Note, that presently no alternative offer exists for the management of preclinical imaging studies, domain where the needs for data and processing pipelines sharing are prominent, boosted by **3R** (Replacement, Reduction and Refinement) principles.

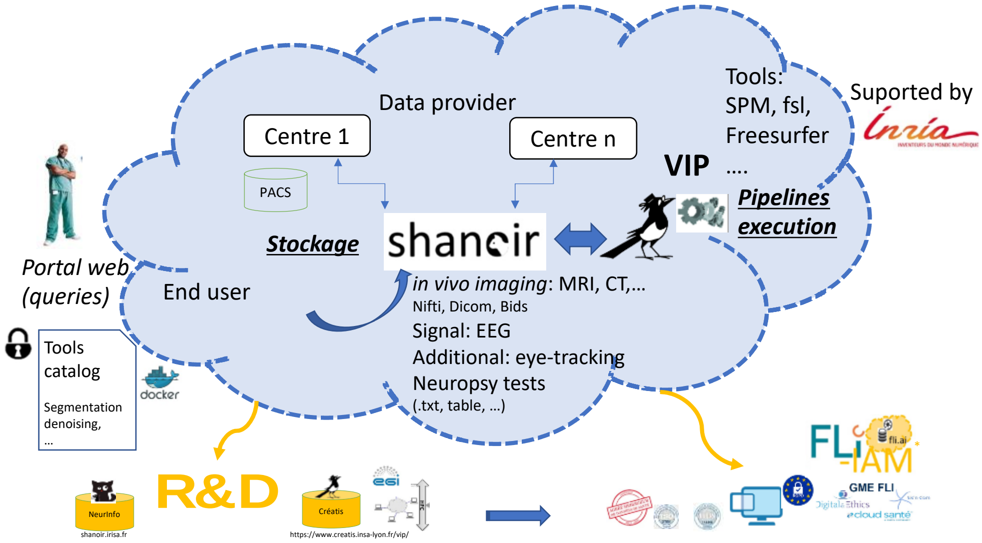

Fig. 3. FLI-IAM architecture is built around to major components Shanoir and VIP. The *R&D* version is hosted by the public partners (Inria and Cnrs) and the FLI-IAM* version is hosted by our industrial partner that owns GDPR and health data hosting certifications for the cloud environment. The innovative *R&D* software extensions are integrated in successive FLI-IAM* updates.

Several actions in this direction are in progress for instance as a partner of the **ANR MUDI4LS** project (Mutualised Digital Spaces for FAIR data in Life and Health Science) for *in vitro* imaging and genetics repositories connections, of **FSM** (Fédération des Spécialités Médicales, project Grand Défi), which records at the national level the procedures for medical interventions, to integrate imaging data in the registers, and of **EBRAINS**, to large the types of data currently stored (including intra cerebral recordings, EEG,..) and extend its usage by hosting large neurosciences imaging projects. As already demonstrated, FLI-IAM* is a dedicated infrastructure to support image processing software competition (challenges) and benchmarking.
We also need to pursue our ***R&D*** efforts to provide a platform customized to the specific needs of the *in vivo* imaging community, notably in extending the catalogue of imaging processing pipelines and machine learning libraries, and offer the optimized and rationalized computational resources required (**AI Green**). Additionally, Federated learning solutions will be tested to bring the algorithms close to the data. The contour of the new private-public partnership (starting at the beginning of 2023) is under construction and its corresponding viable business model.

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6. Perspectives for France Life Imaging

The creation of FLI in 2012 has enabled the financing of a significant number of acquisitions of imaging systems in France. Above all, it has enabled a real networking of platforms, guaranteeing wide access to imaging and maintaining expertise at the highest level.

Ten years after the creation of FLI, maintaining platforms at the highest level requires new investments. These investments are essential to sustain the involvement of the imaging research communities in this collective effort. They are also required to improve platform integration and infrastructure expansion.

6.1 Guiding public decision

Since 2018, the supervising institutions have required FLI a prospective document about the equipment requirements of the French platforms. To that aim, the regional hubs organize regular consultations to identify and prioritize their equipment needs. On the basis of these consultations, the national steering committee synthesizes all the requests, ensuring overall consistency. This makes it possible to draw up a national prospective document that has been regularly updated since 2018.

6.2 Refunding the platforms

The *France2030* call for projects, launched by the government in September 2022, proposes to finance heavy equipment (> 1 M€) related to biology-health infrastructures over the 2023-2030 period. It is a real opportunity to re-equip FLI imaging platforms.

Based on the infrastructure renewal project validated by the international jury in 2019 and FLI's prospective documents regularly updated since 2018, FLI's hubs have worked together to identify the imaging systems they most urgently need to maintain a network of high-performance platforms and foster the emergence of disruptive approaches in imaging.

For the period 2023-2030, FLI will pursue the two objectives that have been guiding its equipment strategy:

1. Maintaining a high-performance imaging instrumental park, accessible to French biology-health research teams to conduct ambitious research projects,

2. Bringing out disruptive approaches in imaging, many of which will be indispensable research tools for many disciplines in the future.

To achieve these objectives over the 2023-2030 period, FLI is requesting a total of 21.6 M€[h] in funding from the *France2030* for a total equipment cost of 45.3 M€. The proposed equipment strategy is therefore largely based on co-financing already obtained or planned. This strategy is based on the expected leverage effect of the *France2030* to significantly renew French imaging equipment. The funding provided by *France2030* will be supplemented by local co-financing. In this way, the equipment roadmap defined by the national infrastructure will prevail, guaranteeing the overall coherence of French equipment and access to the highest level of imaging for the biology and health research communities.

The equipment requested is evenly distributed between that required to maintain a high-performance instrumental park (47%) and that required for the emergence of disruptive approaches (53%).

6.3 Expanding the national coverage by integrating new platforms/hubs

At the time of the renewal of the infrastructure in 2019, the integration of 3 new hubs was validated by the international jury evaluating the renewal file. Currently, we do not have any information about how FLI will be extended after 2024, even if the *France2030* call for proposal reflects the will of the Ministry of Research to continue its support for the infrastructure. In particular, we do not know whether the extension after 2024 will be conditional on the evaluation of a new project by an international jury. Furthermore, FLI does not have a formalized procedure for extending its regional hubs or creating new ones. Therefore FLI is not able to respond to requests from hubs wishing to join the infrastructure.

However, some members of the FLI steering committee have recently been approached by 3 platforms that are not currently part of the 9 regional hubs. These are CYCERON (Caen), IVIA (Clermont-Ferrand) and LIIFE (Lille). An internal reflection must be initiated on how to respond to these requests.

[h] Initial discussions with the supervising institutions showed that a proposal above 20 M€ would unlikely be considered.

7. Program of the Dec. 9 meeting with the BIAB

8.45 – 9.00am	**Closed meeting between experts**	*BIAB members*
9.00 – 9.20am	**Welcome - Introduction to the meeting Overall presentation of FLI**	*Vincent Lebon*
9.20 – 9.25am	**Structuring platforms/equipment nationwide: the 9 regional hubs**	*Vincent Lebon*
9.25 - 9.45am	**Illustration for an initial hub and a newly incorporated hub:** - **Marseille Hub** - **Grand Est Hub**	 *Monique Bernard* *Michel de Mathelin*
9.45 – 11.00am	**Developing scientific expertise: the 4 networks of expertise** **- Network of expertise 1 (10min+5)** **- Network of expertise 2 (10min+5)** **- Network of expertise 3 (10min+5)** **- Network of expertise 4 (10min+5)** **- Leverage effect (10min+5)**	 *Pascal Dumy* *Luc Darrasse* *Michel de Mathelin* *Dimitris Visvikis* *Régine Trébossen*
	COFFEE BREAK	
11.30 – 11.50am	**Developing training (15min+5)**	*Albertine Dubois*
11.50am – 12.15pm	**Offering image analysis and management tools to research communities (20min+5)**	*Michel Dojat*
12.15 – 12.30pm	**Mid-term perspectives (10min+5)**	*Vincent Lebon*
	LUNCH BREAK	
1.30 – 2.30pm	**Discussion with the BIAB**	*BIAB and FLI members*
2.30 – 4.00pm	**Closed meeting (report draft)**	*BIAB members*
4.00 – 4.30pm	**Reporting of the experts**	*BIAB and FLI members*