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Acronyme du projet/ Project's acronym	FBI
Titre du projet en français	France-BioImaging
Project title in English	France-BioImaging
Coordinateur du projet/Project Coordinator	Nom / Name : SALAMERO JEAN Etablissement / Institution : CNRS-Institut Curie Laboratoire / Laboratory : CeMiBIO (Operational National Coordination of FBI)/ Cell Biology and Cancer Numéro d'unité/Unit number : UMS3714/UMR144
Aide complémentaire demandée/ Additional funding request	In long term sustained IR + integration within ERIC-EuBI= 7 M€ (with 2 M€ in 2020 and 2021)
Domaines scientifiques/ Scientific fields	Biological imaging ; image Analysis-BioImage Informatics ; photonic and electronic microscopies; Correlative microscopy; HCS; in depth and Preclinical In vivo Imaging; Probe development –optogenetics;

**Affiliation(s) du partenaire coordinateur du projet (numéro RNSR)/
Coordinator institution**

Laboratoire(s)/Etablissement(s) Laboratory/Institution(s)	Numéro(s) d'unité/ Unit number	Tutelle (s) /Research institution
UMS3714 CEMIBIO	201521729H	CNRS/Institut Curie

**Affiliations des partenaires du projet (numéro RNSR)/ partner
Institution(s)**

Laboratoire(s)/Etablissement(s) Laboratory/Institution(s)	Numéro(s) d'unité/ Unit number	Tutelle (s) /Research institution
CDC;CEMIBIO;PCC/ IJM/ IBENS; PASTEUR/ DC2P/ I2BC ;USR426 ;LOB/ CBS;IGMM;BIOCAMPUS/ IINS ;LP2N; BIC ;LBM/ CIML ;IBDM ;Institut Fresnel	199511677U/ 199411684F/ 199712638E/ 201019092N/ 199812965F/ 199818058S/ 201521299R/ 201521757N/ 200717455X/ 199111979P/ 201119452A/ 200519254L/ 201119489R/ 200511663K/ 200017461J/ 201220316K/ 201220335F	CNRS/Inserm/Inria/Institut Curie/institut Pasteur/ENS Paris/Ecole Polytechnique/Univ. Paris 5, Paris 7, Paris 6 (SU), Paris 11; Univ. de Bordeaux ; Univ de Montpellier ; Univ. Aix Marseille.

1. RESUME / SUMMARY.....	3
2. PARTENAIRES DE L'INFRASTRUCTURE / INFRASTRUCTURE PARTNERS	4
2.1. Institutions Partenaires / partner Institutions	4

2.2. Organisations / Institutions.....	4
3. BILAN / PROJECT REPORT	5
3.1. Réalisé / Achieved	5
3.1.1: Objectifs initiaux du projet / Initial objectives of the project.	5
3.1.2: Réalisation des objectifs / Achievement of the objectives.	8
3.1.3: Prévu versus réalisé : difficultés rencontrées et solutions mises en œuvre / Planned versus achieved : encountered difficulties and implemented solutions.	12
3.1.4: Réponses apportées suite à l'évaluation à mi-parcours / Corrective actions following the mid-term evaluation.	13
3.1.5: Principaux faits marquants et liste des 20 principales publications / Main Highlights and list of the 20 most relevant publications.	16
3.1.6: Indicateurs chiffrés démontrant la plus-value de l'infrastructure / Numerical indicators demonstrating the added value of the infrastructure.	18
3.2. Impact socio-économique / Socio-economic impact.....	19
3.2.1: Retombées pour la communauté scientifique / Impact for the scientific community.	19
3.2.2: Impact pour la décision publique / Impact for public decision-making.	20
3.2.3: Principaux brevets et licences, expertises réalisées / Main patents and licences, expert evaluations performed.	21
3.2.4: Partenariat avec les entreprises et relations contractuelles établies / Industrial partnerships and contractual collaborations established.	21
3.2.5: Formation / training.	22
3.3. Moyens mis en place / implementation.....	23
3.3.1: Organisation et gouvernance / Organisation and governance.	23
3.3.2: Modalités d'accès et tarification / access mode and pricing strategy.	26
3.3.3: Moyens humains et financiers supplémentaires apportés par les partenaires depuis la création de l'infrastructure. / Additional human and financial resources provided by the partners since the creation of the infrastructure.	27
3.3.4: Moyens apportés par des cofinancements / Means provided through co-financing.	28
4. PROJET POUR LA PERIODE 2020-2024 /PROJECT FOR THE 2020-2024 PERIOD	29
4.1. Présentation synthétique des arguments pour une pérennisation de l'infrastructure/ Synthetic presentation of the arguments for the longer term continuation of the infrastructure.....	29
4.2. Principales évolutions envisagées / Main planned evolutions...	30
4.2.1: Nouveaux développements justifiés par des avancées scientifiques et technologiques / New developments justified by scientific and technical evolutions.	30
4.2.2: Changement du périmètre et services proposés en fonction des avancées scientifiques et techniques ou des besoins des utilisateurs / Changes in scope and in services offered due to scientific and technical evolutions or User needs.	31
4.3. Impact du maintien de l'infrastructure nationale / Impact of maintaining the existing national infrastructure	33
4.3.1: Sur la communauté Scientifique Nationale / Within the National Scientific community.	33
4.3.2: Sur la stratégie de la France à l'international / On France international strategy.	35
4.3.3: Dans le domaine socio-économique / In the socio-economic field.	36
4.4. Organisation en vue de la pérennisation de l'infrastructure / Organisation with the perspective of sustainability	37
4.4.1: Evolution organisationnelle des structures de gouvernance souhaitée / Expected changes in the governance structures.	37
4.4.2: Evaluation / Evaluation.	38
4.4.3: Besoins en termes de ressources en personnel / Identified human resources needs	38

4.4.4: Mécanismes de financement de l'Infrastructure / Funding mechanism of the infrastructure.	39
4.4.5: Politique de valorisation / Economic Valorisation policy.	40
4.5. Demande budgétaire / budget request	40
4.6. Engagement des tutelles partenaires / Involvement of partner institutions.....	40

1. RESUME / SUMMARY

Rappel du domaine d'intervention de France BioImaging

Une compréhension approfondie des processus de la vie s'appuie sur le développement de nouvelles technologies permettant l'observation multi-échelles des systèmes biologiques. France-BioImaging est l'Infrastructure nationale, distribuée et coordonnée de l'Imagerie Biologique. L'objectif général de France-BioImaging est de fournir à tous ses utilisateurs (biologistes pour la plupart, mais également chimistes, physiciens, mathématiciens et informaticiens qui s'intéressent au vivant...) un accès immédiat à des mesures quantitatives pertinentes et de faciliter une compréhension intégrative des activités cellulaires et physiologiques. FBI rassemble, dans une infrastructure coordonnée unique, 11 plates-formes d'imagerie de haut niveau (10 en 2018, après regroupement sur Montpellier ; dont 9 IBiSA + 1 en cours de labellisation) soutenues par des laboratoires de recherche et développement de niveau mondial.

Missions. Notre tryptique « Innovations-formations-accès »

- (i) disséminer et inventer les nouvelles technologies d'imagerie,
- (ii) élargir le portfolio de formations vers les utilisateurs et vers les personnels en charge de ces approches,
- (iii) les rendre accessibles au plus grand nombre.

France BioImaging's field of intervention

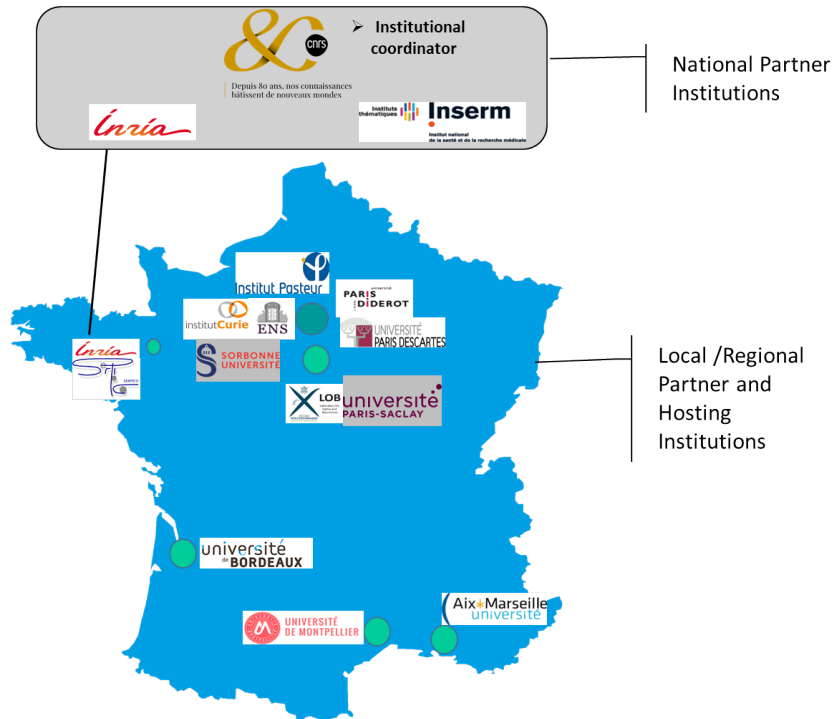
A thorough understanding of life processes is based on the development of new technologies for multi-scale observation of biological systems and quantification of dynamic processes. France-BioImaging is the national, distributed and coordinated infrastructure of Biological Imaging. The general objective of France-BioImaging is to provide all its users (mostly biologists, but also chemists, physicists, mathematicians and computer scientists interested in life sciences) with immediate access to relevant quantitative measurements and to facilitate an integrative understanding of cellular and physiological activities. FBI brings together, in a single coordinated infrastructure, 11 high-level imaging core facilities (10 in 2018, after consolidation in Montpellier; including 9 IBiSA + 1 undergoing certification) supported by world-class associated research and development teams.

Missions: Our tryptic "Innovation-Training-Access"

- (i) Disseminate and invent new imaging technologies,
- (ii) Expand the portfolio of training courses for users and staff in charge of these approaches,
- (iii) Make them accessible to as many people as possible.

2. PARTENAIRES DE L'INFRASTRUCTURE / INFRASTRUCTURE PARTNERS

2.1. INSTITUTIONS PARTENAIRES / PARTNER INSTITUTIONS



-The CNRS is the **coordinating institution**. It covers all FBI nodes and provides most of the human resources. The CNRS is the main beneficiary of the IR FBI.

-INSERM and INRIA are **national partner institutions**, Inserm also covers all nodes, on a weaker steering wheel than CNRS. Inria, at this stage, is involved in the BioImage Informatics Transversal Node (IPDM) through the Serpico laboratory of the "Bretagne-Atlantique" Inria Centre.

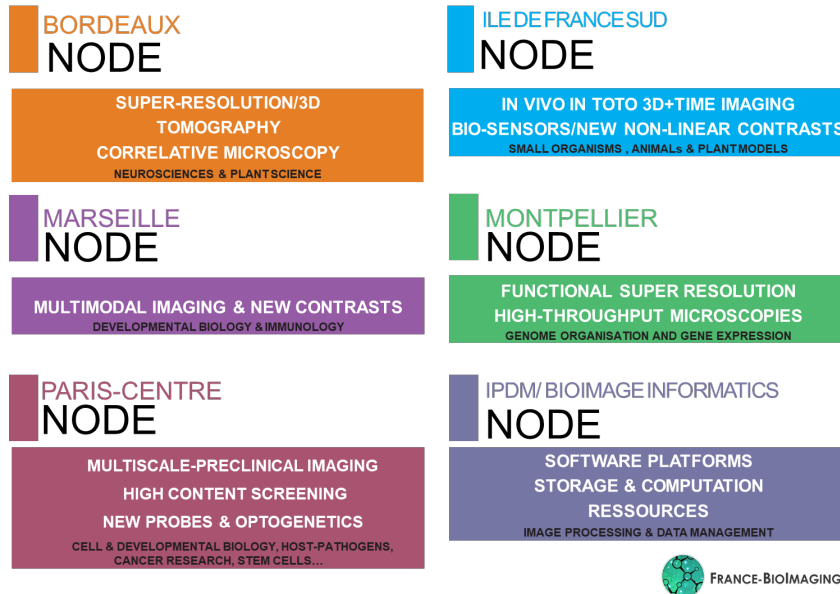
-Institut Curie, Ecole Normale Supérieure (also in PSL U), Institut Pasteur, Paris Descartes & Paris Diderot (University of Paris in 2019), UPMC (SU) are **partner members and host institutions** of the Paris-Centre node. They support the FBI in all financial aspects at various levels (Institut Pasteur is a unique founding organization for FBI@Institut Pasteur).

-X-Ecole Polytechnique is a **partner member of IdF-Sud**. Paris Saclay, is **not part of the FBI consortium agreement**. However, it is a local support entity for IdF-Sud Node.

-The Universities of Aix-Marseille (AMU), Bordeaux (BU), Montpellier 1 and 2 (MU), are all **Regional Partner and Hosting Institutions** that support their respective nodes in their various local aspects.

2.2. ORGANISATIONS / INSTITUTIONS

Within the rather complex landscape described above, the **France BioImaging RI** acts as an element of rationalisation and pooling in the field of biological imaging in France. A "corporate" activity at local and national level, which gives international visibility to all **partners**. Below is illustrated the rational of the distributed nature of the IR; technological and methodological offers and expertise match with specific excellence of the Nodes in Life Sciences domains.



3. Bilan / Project Report

3.1. REALISE / ACHIEVED

3.1.1: OBJECTIFS INITIAUX DU PROJET / INITIAL OBJECTIVES OF THE PROJECT.

France-BioImaging (FBI) was the laureate of the call “National Infrastructure in Biology and Health” in the frame of “Investments for the Future” (PIA 1) in 2011. It was built on a national initiative to support the access to innovative imaging approaches in France to a wide scientific, medical and industrial community. As a consortium, five distinct geographical Nodes were identified on the basis of first, identified relationship between developers of new imaging approaches (R&D labs) and large imaging core facilities, that already answered the IBiSA criteria (see <https://www.ibisa.net/>) and second, with a specialization of a local expertise in main biological topics. This crossover between imaging technologies and expertise in scientific topics is still relevant and a characteristic of the complementarity between the FBI Nodes.

Full understanding of life processes relies on the development of new technologies enabling the multiscale observation and quantification of biological systems. At the frontier between molecular, cell and development biology, biophysics and engineering, mathematics and bioinformatics, France-BioImaging gathered, in a coordinated infrastructure unique in France, several outstanding Imaging Facilities supported by laboratories for state-of the art R&D with the aim to cover recent advances, in all domains of microscopy, probe engineering and to provide quantitative measurements, computational analysis and an integrative understanding of a wide range of cellular and physiological activities, within simple biological models up to small animals, in normal and pathological situations. The ultimate goal of France-BioImaging was thus to give faster access to advanced imaging techniques and methods to a wide national scientific community and also to the socio-economic development through industrial partnerships and transfer of innovations.

In order to do so, FBI was built on already existing Imaging Core Facilities, **basically the same number and locations** as today (except for the integration of new services). All infrastructure Nodes and

almost all Sites have CNRS-related components. FBI is also supported by many other scientific institutions and some universities. France-Biolmaging was expected to represent the national structuration in the "Euro-Biolmaging project in the roadmap of ESFRI (European Strategy Forum on Research Infrastructures; ESFRI project in 2010).

Among new bio-imaging technologies and methodologies, that we targeted as necessary offers for the overall community of users,

Super Resolution and Single Molecule Tracking approaches were critically missing in 2011, in France, while optical microscopy has been already transformed by the development of "nanoscopy" techniques, which permit imaging of living cellular structures and molecular dynamics with a resolution approaching a few nanometers. These techniques were either based on the localization of single molecules) or engineering of the optical transfer function / point spread function of the microscope in wide-field or laser scanning microscopy).

Functional Imaging was also identified as a field of interest, where conceiving, developing and applying advanced imaging methodologies appeared to be required to investigate biomolecular function, interactions and dynamics in complex environments, spanning from "in vitro" systems, to bacteria, eukaryotic cells, and living organisms. We thus focused on photonic tools that allow to measure molecular diffusion and dynamics, molecular interactions, and we developed advanced data analysis and modelling methods in this respect.

CLEM & SuperCLEM. We also anticipated an increasing interest for new "Correlative Light and Electron Microscopy (CLEM)" and the development of innovative methods to achieve a workflow of integrated observations from data obtained on cells and tissues in health or pathological conditions (cancer, lysosomal and neurodegenerative diseases, phytopathology).

New contrasts and in-depth imaging. We first aimed at developing innovative photonics tools to perform in depth imaging in microscopy and endoscopy. Two axes were worth to explore. The first one focused on new contrast generation that do not rely on conventional refractive, absorption or fluorescence contrast mechanisms; the second one aimed at developing new methodologies and instruments that could extend the imaging depth of conventional microscope.

High Content Screening (HCS) to systematically study phenotypes of cells or organisms in varying conditions. HCS relied on a very high degree of automation regarding sample preparation and microscopy and requires specialized and robust methods for automatic data analysis, meaning dedicated tools for data handling. We envisioned a tremendous development of such approaches, both for the improvement of the data acquisition (integration of innovative imaging approaches) as well as in data mining involving machine learning and further deep learning methodologies.

Probe Development, Optomanipulation & Optogenetics. We also aimed at establishing state of the art chemical technologies for the optical control and reading out of living systems associated with new optical methods of excitation beam shaping. Our initial goal and somehow a challenge at that time in France, was here to establish a primary "**collaborative framework**" gathering chemists and cell or developmental biologists.

BioImage Informatics–Image Processing and Data Management. This was the only Transversal node of our proposed Distributed Infrastructure or in other words, both a **Node and a Working Group**. It was aimed at addressing all questions related to the computerized analysis and handling of bioimage data. We developed several lines of development: 1. image processing and analysis solutions for data

quantification and modeling; 2. Pilots in image data archival and retrieval; 3. high performance infrastructures dedicated to massive computational demands.

For all these aspects which corresponded to the **Instrumental and Methodological Work Packages**, we created dedicated **Working Groups** which underwent modification over time (*See Annex 2. Supplementary information-updated WPs/WGs in 2019*) gathering both specialists and personals of our Core Facilities (Scientists and Engineers). The goal was of course to challenge innovative technologies and methodologies by the expectations of an infrastructure devoted to serve a large number of users, with a broad diversity of biological questions. At the end, to install the most useful technics on the best places merged with the best expertise available, for answering scientific topics.

One of the main challenge, was to harmonize and coordinate as much as possible the practices and procedures of the Core Facilities, constitutive of the distributed infrastructure, as well as their access, which depended on very local environment, sometimes below the regional or hence, the national Scope. Another **Working Group** was created which addressed three coordinated activities of the **management WP** on “**Training, Dissemination & Technological transfer**” with objectives indicated below and which progressively gained importance, justifying to strengthen the National Coordination over the years since the middle of 2015.

Dissemination, outreach & Training

At the National Level (node and inter-node) with, 1) Extended support for existing Core Facility management tutoring: metrology, quality management, purchasing, etc.... 2) Support, co-organization, or organization of conferences, training and education activities, with the constant concern to “not reinvent the wheel” 3) propositions for FBI specific trainings to implement

At the International Level to, 1) Maintain and reinforce the involvement of France in the Euro-Biolmaging WPs dedicated to Training. 2) Insure France-Biolmaging presence and visibility in the international landscape related to biological imaging and 3) participation in European consortium for training programs in H2020.

Technology transfer

With the aim to make propositions to coordinate/facilitate inter-nodes collaboration program, proof-of-concept studies at the national and international level, technological transfer and exchanges between industrials and academics,

1) By extending **access of confidential premises** and facility for collaboration between industrials and academics. (*note that ANR-LabCom program was opened in 2013*) 2) By Fast help in development or integration of « ready to go » technologies (when PoC is done) 3) Through small and adapted funding of equipment (new detector, illumination source, optical modules....), to put pre-competitive photonic components and systems in user’s hands 4) By funding for travelling, short term journey fellow exchanges between Labs/Advanced Core Facilities, Labs/Labs, or Core F/core F.

The **National Coordination** was in charge of managing the funding of these transverse activities, while more focused dissemination or training activities were proposed to be managed by local Nodes. Evaluation/Decisions were made regularly during the Executive Committee meetings.

3.1.2: RÉALISATION DES OBJECTIFS / ACHIEVEMENT OF THE OBJECTIVES.

France-BioImaging is above all an infrastructure intended for Research, but whose impact goes beyond academic research. The technologies proposed, developed and successfully disseminated within the FBI scope are of major importance in the scientific and societal challenges of the Life Sciences (stem cell biology and regenerative medicine, studies of marine organisms and their development/evolution in a constrained environment, host-pathogen interaction, cancer, immunology, neuroscience and degenerative diseases...). In all these fields, from cell biology to preclinical investigations, only the integration and rational availability of the best technologies, methodologies and expertise in biological imaging can and will answer emerging scientific questions. Our activity was therefore aimed at multiple thematic perimeters whose objects of studies are understood on multiple scales and to which we respond with techniques, methodologies and expertise in biological imaging.

However, there is a necessary proximity between installations and objects of study (the cellular "living", model organisms and small animals). FBI Core Facilities respect this rule and serve a first circle of users in their local/regional perimeter. It is why FBI is a distributed research Infrastructure. FBI also responds to demand beyond this first scope. More precisely, the FBI intervenes beyond the regional perimeter, in national and international space, when the equation "bouquet of technologies/expertises/thematic environments" is no longer solved, or more simply, when the "local" no longer meets the user's needs.

FBI intervenes also globally on national actions of knowledge dissemination, training, of platform operators whether they belong to the FBI perimeter or not, of its users by proposing an integrated portfolio of theoretical and practical sessions, based on an already extensive catalogue, available in its various nodes (implemented in 2017-2019).

On its various activities, FBI also demonstrates its international attractiveness, as indicated by a growing number of external users and foreign collaborators (*see Annex 2. Supplementary information. –IMPACT STUDY. International statistics*). Finally, the importance that FBI represents in attracting and recruiting the best teams at its Nodes and Sites must be highlighted and deserves recognition by Institutions. This strategy could only be implemented through the PIA's INBS program, which made it possible to "update" the devices available on FBI platforms at the highest possible level or by implementing emerging and innovative technologies. Most of our achievements will be indicated quantified and commented in the section 3.1.6: NUMERICAL INDICATORS DEMONSTRATING THE ADDED VALUE OF THE INFRASTRUCTURE. Here are mentioned some general implementation over the Project period.

Evolution of the operational structuring the infrastructure: the National Coordination has been responsible for the operational construction and animation of the infrastructure by bearing its management on scientific, administrative and financial aspects, inventories of equipment, human resources and activities; rules of governance and support; design of communication tools; building and animation of the France-BioImaging Community. Important steps in this respect, were the final signatures of the **Consortium Agreement in 2014**, and the creation of a **Service Unit for the FBI National Coordination** in 2015 (UMS 3714 CNRS-Institut Curie). The creation of this **coordination body** was of the utmost importance when considering the weight of administrative work that was

not anticipated initially. This Unit, directed by a DR CNRS, was supported by an administrative officer and a communication officer hired on short term contracts since the middle of 2015 **up to June and September 2018, respectively.**

Main Technological and Scientific Achievements; Dissemination, opening, FBI team building effect

In Super Resolution and Single Molecule Tracking. New approaches in super resolution microscopy (Nobel Prizes in Chemistry, 2014), allowing one to get around the physics barrier of optical resolution, were at the heart of FBI technological achievements. Most current High Res. and SMLM modalities were installed in all Nodes end of 2016, providing Users with state-of-the-art technologies in super resolution imaging. This has been accomplished by both the purchase of commercial microscopes in all FBI core Facilities and the transfer of setups from R&D associated Labs onto these imaging platforms. This also implied new types of services, for preparation of biological specimen or the development of adapted image analysis. Access to these techniques can be considered as one of the main achievements of FBI. **WGs** also tackled technological challenges still to be uncovered in this field. Unique innovative methods were developed such as combining STED and single molecule localization (SML) microscopy on a single microscope platform (IINS Bordeaux Node), high axial resolution using Variable Angle TIRFM or multi-focus microscopy (MFM) in Paris Centre- and Montpellier-Nodes) combined to Super Resolution by controlling beam diffraction pattern for ultrasensitive multicolor PALM (Paris Centre-PCC and Montpellier Node-CBS). A new instrument based on MFM to acquire SMLM images of thick samples with high time and space resolutions was built in Montpellier Node in Collaboration with Paris Centre node (Institut Curie). An MFM/STORM system is now open on the FBI-PICT at Institut Curie. In collaboration with the **BI-IPDM node** (Inria Rennes), a workflow for automated spot detection up to 3D reconstruction and visualization for Multi-Angle TIRFM data is accessible on <http://serpico.rennes.inria.fr/>. In the LOB-Ecole Polytechnique (Idf-Sud Node), the FBI budget was used to co-fund the development of an automated, application-oriented microscope optimized for single-particle experiments.

In summary, if one wishes to measure the impact of FBI in terms of transfer of these cutting-edge technologies to Users, it is worth measuring that MFM, SIM/TIRFM, Multi-Angle TIRFM and other innovative SIM/PALM/STORM or STED/STORM approaches are **all operating and accessible to users** on FBI-Imaging Core Facilities, in Bordeaux, Montpellier, Marseille and Paris-Centre.

From Functional Imaging to Multimodal, New Contrast and In-Depth Imaging. FBI provided key funding for several developments in fluctuation and spectroscopic approaches. Montpellier Node, some sites at Paris Centre and Marseille Nodes, have pioneered the use of scanning fluorescence correlation spectroscopy (FCS, FCCS) and single-molecule FRET methods to directly measure absolute protein numbers and conformational transitions in live cells. However, major investments in this area were carried out before the creation of FBI, which just helped in making them open to the Users, by promoting their integration onto imaging platforms by training platform engineers who now assist users on these setups. The level of maturation already achieved combined with a good match in the rate of Users versus Hours of Accessibility, led us to **close the WG Functional Imaging** in 2018.

At the same time, associated R&D labs were (since 2017) concentrated on innovative developments in multimodal nonlinear microscopy on prototypes. Multi-modal imaging has been strongly developed in the Marseille Node and includes a combination of innovative microscope instruments, such as super-resolution and polarization resolved fluorescence microscopy, nonlinear imaging including CARS and SRS. Strong efforts were engaged in in-depth tissues imaging and opto-manipulation. FBI developed unique innovation in beam shaping, i.e. multi-plane spatiotemporally-focused patterns methods. These developments are applied mainly to brain activity measurements through optogenetics tools or to whole-brain functional imaging (Paris-Centre) with two-photon light-sheet microscopy (IdF-Sud). In addition to these innovative techniques, other non-linear microscopy systems were set up on FBI Imaging Core Facilities for longitudinal studies in intravital microscopy in small animals, in the field of cancer research and neurosciences (IBENS and Institut Curie, Paris Centre). Those approaches and Services include imaging modalities allowing non-invasive probing of the biological microenvironment (SHG, THG...)

From development of Light Sheet Illumination approaches up to the creation of the WP (and WG) Multi-Scale light Sheet Microscopy. In the time course of the FBI project, many In-house designed light sheet microscopes (DSLM) were set up, transferred to platforms and opened to users in multiple locations (Paris Centre, FBI-Imagoseine, FBI-PICT; Marseille, FBI-PicSl). A combination of DSLM and Spinning disk microscope (started in 2017) was further developed in Paris Centre (available on FBI-PICT-Curie) through collaboration between IJM and Institut Curie teams. In Paris Centre, Institut Pasteur and Institut Curie, proposed a joint project at the **Sesame Program of the Ile De France Region-2016**, named **“Multi Scale Light Sheet Microscopy”**, with the aim to provide all possible modalities using light sheet illumination to the users. This program was largely based on FBI collaborations beyond the Paris-Centre node (with Bordeaux IINS). While the project was not funded, it was a first step toward a **new WG**, finally launched in December 2018 (**WG1b “Multi-Scale light sheet Microscopy”**).

In CLEM, SuperCLEM, cryoCLEM. Development of correlative approaches with best compromise for space-time resolution in LM-EM correlation has been settled, notably in Paris Centre Node. It includes development of tools for sample handling, for image registration (Ec.CLEM software through ICY, with IPDM-node) and the development of a new fast automated High Pressure Freezing system coupled to spinning disk confocal microscopy (through a partnership with a French newly created Startup, *CryoCapCell*). At Institut Pasteur, different CLEM approaches are developed: super-CLEM by correlation of SEM and SIM, based on 3D Focused Ion Beam SEM (the only system of this type for biological applications in all Ile de France) and CL-SEM for cell imaging in cryo conditions (in progress). Super-CLEM/3D SIM experiments were performed at IBENS. SBF systems are now installed in Paris Centre, Marseille and Bordeaux Nodes. Many other projects in this domain are going on.

In BioImage Informatics and Data Management (linked to HTP & High Content Screening). New Image processing suite and analysis tools, developed by the Transversal BI-IPDM Node partners, are simply impressive. Their dissemination through common and/or open software platforms or web services (Icy, Mobylye@Serpico and OpenMole), was an asset for the international visibility of FBI. It is

important to mention that FBI co-funded access to grids and clusters, notably by renting computation access (National infrastructure, France-Grille). Statistics and publications (**best FBI cited publications in WoS**) reflect the success of **the BI-IPDM transversal node**.

However, efforts in this fruitful domain should be reinforced in the future, when considering the deluge of data the new imaging technologies are producing these days (up to a few Tbytes/day in DSLM). During the last years, technological advances in automated microscopy and software, together with an ever-growing pool of available collections of genetic tools have allowed the development of HTP functional genomics and high-content imaging systems that exploit the power of genetics in a systematic way. The Montpellier Node implemented a high-throughput, high-content pipeline for sample preparation, image acquisition and analysis, a service fully funded by FBI (SmFISH). The main activity of Biophenics (HCS platform part of the FBI-PICT) in Paris Centre is to support researchers in assay development and optimization for HCS with chemical or siRNA, mainly for cancer related biological processes, while an FBI Associated team of the **Computational Biology Center at Institut Curie**, develops methods for HCS data analysis, combining **image analysis, deep learning and data mining**. **HCS platforms in Paris-Centre** are fully complementary in their methods and instruments. They collaborate, communicate and Users are now referred one to another, depending on how the project fits with the required expertise. Interestingly, both FBI-PICT Biophenics and UTechS-Imagopole are also members of the recently launched **INBS-IR CHEMBIOFRANCE** (on the RI roadmap of the French Ministry since 2018) devoted to the discovery of bioactive molecules. This demonstrates the importance **to integrate innovative imaging approaches with genomics and structural biology** for the characterization of new biomedical targets.

In Probe Development, Optomanipulation & Optogenetics, Beside technological development, new chemical technologies for optical control of living systems are crucial. A series of important work has been first published. They relate respectively to (i) the selective imaging of photo-convertible fluorescent proteins, (ii) the photo-activated fluorescent proteins with Three-Photon excitation (iii) a study on the photo-degradation of proteins. The development of sensors is directly related to improve imaging methods and to the emergence of a variety of techniques of photomanipulation. Different types of probes are associated with different techniques, today developed in France Biolmaging: (i) nano-markers are used in electronic and photo-thermal correlative microscopy (Paris-Centre and Bordeaux Nodes), persistent luminescence nanoparticles were used to observe long-term living samples (Paris Centre); (li) biosensors measures spatiotemporal subcellular biochemical activities of proteins such as Rho-GTPases (IdF-Sud, Paris Centre); (lii) the probes and methods for optogenetic techniques (photoactivation/inactivation/cell signaling control) (Paris Centre; Marseille; IdF-Sud, Bordeaux). Associated with optical methods for excitation beam shaping, these approaches allow the control of protein function by light. They provide an alternative to genetic or pharmacological conventional methods and provide information about the function of proteins at high space-time resolutions. Today, chemists are among the most successful in the FBI-community in terms of Scientific Impact (*see IMPACT disciplines metrics in the Annex 2. Supplementary Information* and section 3.2.3: MAIN PATENTS AND LICENCES. Works supported by the FBI program, led to the creation of startup companies (*Twinkle Bioscience*, as an example). We consider the integration of chemists' knowledge and know-how as a **"success story"** within FBI achievements.

Progress in technology accessibility. Although the core facilities and teams composing FBI were obviously already active prior the creation of FBI, one may consider that FBI operation only started once a first set of new technologies were acquired through the FBI funds, either directly purchased from providers or developed in the R&D labs or core facilities, sometimes through industrial partnerships. A large majority of these technologies are related to microscopy setups, other to Information Technology (IT) and innovative methodologies in BioImage Informatics, some to biochemical and chemical characterization and synthesis. In most cases, equipment were already accessible to a broad research community at the end of 2013, thanks to the efficiency of the Imaging Core Facilities, members of the FBI consortium.

3.1.3: PREVU VERSUS REALISE : DIFFICULTES RENCONTREES ET SOLUTIONS MISES EN ŒUVRE / PLANNED VERSUS ACHIEVED : ENCOUNTERED DIFFICULTIES AND IMPLEMENTED SOLUTIONS.

As a first difficulty, the proposed “PIA” funding was **reduced from 37 M€ to 26 M€**. The Head of Nodes and the Coordination made the choice to focus on the replacement of microscopy systems and implementation of new setups (**see 3.1.2 Achievements**), in order to make up for the backlog in access to these technologies in France. As a result, a reduced budget for the implementation of a common data processing and management strategy was allocated. The IPDM node focused more on the development of image analysis software and platforms, and less to the Data Management requirements.

Another early difficulty rose from unexpected financial rules (specific for the INBS AAP 2010). The whole allocated budget had to be divided between each Node from the beginning. The initial transversal node, BioImage Informatics-Image Processing and Data Management (IPDM), was built on a scientific basis and gathered partner institutions without link to CNRS (Institut Pasteur/Inria). Thus, all financial annexes had to be modified and these novel Partner institutions had to be created, delaying to middle of 2012 the signature of the conventions between the French National Research Agency (ANR) and the different hosting institutions. Due to these administrative and financial issues, investment started in 2013.

We will not hide that the major difficulties encountered throughout the project are linked to the recurrence of requests of reports from the various institutions in charge (ANR, CNRS, DGRI Ministry...) which are sometimes similar but not identical in their formulation. Combined with the administrative burdens imposed by dispersed financial management structures, poorly coordinated and rarely aware of the INBS-PIA program, the lack of stabilized support staff within the RI (fixed term contract to be renewed every year, for a maximum of about 3 years), it has greatly hindered the implementation of a rationalized cohesion of the RI. The **long term continuation of the FBI Research Infrastructure** will clearly depend on more direct access to its budget. It will require allocation of permanent human resources by institutions in charge and/or a “legal status” that will allow some independency and flexibility, at least in the recruitment of support human resources. Which legal entity status would be most adapted, needs to be discussed with our **Institutional Committee**.

3.1.4: RÉPONSES APPORTÉES SUITE À L'ÉVALUATION À MI-PARCOURS / CORRECTIVE ACTIONS FOLLOWING THE MID-TERM EVALUATION.

The mid-term evaluation panel considered that FBI's functioning does not correspond to that of an infrastructure for two reasons: 1) the lack of consideration of operating and staff costs, and 2) the lack of cohesion and synergy between network partners and users. The panel recommended to: 1) improve governance to define and implement a credible business model beyond of the agreement period and 2) develop links between the various partner sites, as previously requested in 2010 by the selection board.

Action plan and solutions to improve cohesion and synergies between network partners and users

We realized that answers to most of the recommendations needed a change and a reinforcement of governance and coordination. A first version of a "new governance" was proposed to our Institutional Committee, in May 2017. Following the discussions, a new governance scheme was proposed and validated by the Institutional Committee and following some clarifications, approved by the RIs CoPIL, **finally in June 2018**, allowing the continuation of the ANR financing process.

The precise organization and the missions of the actual governance bodies will be detailed in section **3.3.1: ORGANISATION ET GOUVERNANCE / ORGANISATION AND GOVERNANCE.**

Some new implementations and expected changes, related to our recent integration into the European Infrastructure ERIC-EuBI, better sharing of responsibilities or tasks, and modifications of the institutional perimeter, are also proposed in our "**FBI governance organizational chart**" and a number of requirements are mentioned in section **4.4.1: EXPECTED CHANGES IN THE GOUVERNANCE STRUCTURES.**

The main elements of this **governance scheme** tends to:

- o Better take into account the needs of the various types of infrastructure users (industrial and academic),
- o Increase synergy between the communities of the different Nodes, between coordination and them, between all "user" communities, beyond the FBI Centres located on the nodes,
- o Establish a viable economic strategy based on the development of dedicated missions for the coordination and integration of projects proposed by the various parties constituting the infrastructure.

The composition and tasks of the **National Advisory Committee** have been thoroughly reviewed after 2016. It is now reinforced by the **National User Committee, the Tech Watch Committee and the FBI Industry Committee**. The main modification concerned the composition of the "**National User Committee**", now composed exclusively of users outside the FBI scope, in order to guarantee its independence.

The members of this Committee were first all met in 2017. A list of questions was proposed to them before the meetings, leaving a large part to their prospective reflection on the need in terms of service provision and access to biological imaging technologies.

Their comments were then used to:

- 1) the implementation of a series of **online " user surveys"** (priorities in terms of service quality and new services, of technological access, needs in data management and analysis...),

- 2) define the locks to which the infrastructure must strive to respond in accordance with the terms of the offer,
- 3) complete the feedback from the "local user committees" (whose have always been larger than "on-site" users committees) in place on all of the 10, then 11, FBI platforms.

The information collected highlighted three areas for improvement and one general comment.

Briefly they concern

A "user" communication plan capable of better informing user communities about the entire FBI infrastructure offer seems necessary. Our communication tools "website, newsletter, participation in various general and specialized symposiums" were clearly to be improved. **All actions undertaken are presented in (Annex 2 Supplementary Information)**

A strong need for training. In 2018, a "training officer" was recruited in the person of Caroline Thiriet, previously hired during the **EuBI preparatory phase II** on a similar mission, with the task to plan and define the FBI Training "**strategic plan and business plan**", in conjunction with the relevant departments of our various supervisory institutions, our industrial committee and scientific societies (**See Annex 2. Supplementary Information-TRAINING**) and in the perspective of our integration in the ERIC-Eurobioimaging in 2019. Our aim is to propose a rationalized *portfolio* that will answer quality criteria, be exportable, and allowing both users and core facility staff to validate acquisition of knowledge. This will be explained in details, in the section **3.2.5: / TRAINING**.

A very strong call, but rather poorly defined for help in data analysis, bringing together under the same theme, training, expertise in processing, quantitative analysis (detection, monitoring, classification, etc.), workflow building and management of the flood of imaging data, linked to technological progress (multi-dimensional acquisitions, resolution, sensitivity, etc.) in our field. (**See Annex 3. Online surveys and Inquiries**). This need is at the first rank of our priorities. It justifies a **dedicated mission** on defining further our **DATA management plan** in order to reach adoption, notably by biologist Users, of the "FAIR" principles.

Interestingly, "external users" considered access to technical devices and associated expertise in the infrastructure to be "**highly relevant to their needs**". This "*National User Committee*" complements the "*Local User Committees*" of the ten (eleven since 2017) FBI platforms. Their recommendations **in terms of technological and methodological needs** defined our proposals in our "**PIA3 Priority Equipment**" requirements, returned to the Ministry (2017, 2018) and CNRS in 2019 (**see Annex 4. FBI Next Generation PIA3/AMI**).

We also created an "**FBI Industry Committee**". Representatives (President and Vice-President) were invited four of the monthly meetings of the Executive Committee, in 2017-2018. Its original composition and missions will be developed in section **3.3.1: ORGANISATION AND GOVERNANCE**.

Actions and decision-making centralization to strengthen cohesion within the FBI consortium

We will detail only a few among new actions since 2016, in order to clarify their rationale.

Node Communities. In order to define a "Node Synergy" strategy and to respond to the future needs of the user communities, we have set up a list of "agents of liaison for technical information gathering and communication" and a dedicated group in the National Coordination composed of the

Node Community Officer, the Communication Officer and the Scientific Coordinator. The new "Operational Manager", recruited in 2019, joined the group, as the Operational Director. This group organizes thematic visits to sites and maintains regular communication with local referents. **Back in 2017-2018:** the last series of site visits, combined with two other actions of the same type undertaken in 2016-2017 (DATA and Training), have allowed us to define a strategy between the different sites and FBI nodes. The rationale is as follows,

Strengthening inter-Nodes consultation and Centralization of strategic decisions. At the national level, the collected elements constituted the framework of our proposals for a PIA3 project (*see Annex 4. FBI Next Generation.PIA3*); 3 deposits concerted at the AO IBISA 2017 prioritized to the **Nodes Marseille, Montpellier, Bordeaux**. In 2019 a similar consultation took place for Core F of Ile-De-France Nodes (**Paris-Centre and IdF-SUD**). The latter correspond more to the planning of renewal of the first set of equipment acquired in 2013 and to the demand of IBISA label for **two new Core Facilities/services** already belonging to the FBI-Scope (Pasteur "**UtechS PBI-Ultrapole**" and Polytechnique "**Morphoscope**"). We proceed to validations by the Executive Committee (during monthly meetings) extended to representatives of the three structures that make up our "**National Advisory Committee**" (voice consultative).

Strategic plan of investments/equipment within the infrastructure. This plan is updated in broad terms every year, during the "Node and Site Managers' Days" (last, on 5 and 6 April 2018) and should be validated in the future by the **Steering Committee**. Decisions concerning the scientific animation of our community, the procedures for responding to and validating requests for access to external projects or training programs are taken on a "run-of-river" basis during the monthly meeting of our "**Executive Committee**".

At local/regional and thematic level, such actions are complex. It should be noted, however, that most of the deposits for tenders by the nodes and sites that make up the FBI infrastructure, at regional structures or charity associations (FRM, ARC, Leagues...), are claim ownership of the infrastructure and are escalated to the level of the National Coordination and the EC. One of the very last and successful example in 2018-2019, was the funding of the "CryoEM/Live CLEM" project proposed to the SESAME program of Ile de France, as a concerted program between three FBI-Core Facilities in Paris-Centre (FBI-PICT, FBI Utechs PBI, FBI-Imagoseine) supported by three main institutes (Institut Curie, Institut Pasteur, Institut Jacques Monod). In order to strengthen the coherence and cohesion of these activities, FBI is moving towards the generalization of this strategy and also offers its "**panel of experts**" for the evaluation of regional proposals in its domain (Some DIM-IdF, for example). However, because our scope does not cover all part of the national territory, it is still difficult for us to harmonize these different levels of support for funding decisions. Somehow, it justifies our strategy to oversee enlargement of our scope in the future (see section **4.2.2: CHANGES IN SCOPE AND IN SERVICES OFFERED DUE TO SCIENTIFIC AND TECHNICAL EVOLUTIONS OR USER NEEDS** and *Annex 2. Supplementary Information*). When these proposals concern the structural aspects of the national infrastructure, the opinion of our international SAB is required. Finally, these proposals and SAB opinions are submitted to the **Institutional Committee (future Steering Committee), which is decision-making.**

Improve governance to define and implement a credible business model beyond of the agreement period taking into account the consideration of operating and staff costs

A first compilation and simulation carried out in 2018, by Mrs Corinne Tessier, "Administrative Management and Piloting Assistance Officer" of the FBI, was further readjusted. It was a **low estimate**, based on the budget and the structure of the expenditure over the period 2014-2016 and the two first years over the period 2017-2019. **This was appreciated and validated by "The Steering Committee (CoPIL)" in June 2018.**

See ECONOMIC MODEL AND CLARIFICATION OF THE OPERATING BUDGET (DETAIL OF APPROPRIATIONS, ASSESSMENT OF REVENUE, ETC.) AS PART OF THE FBI ACTION PLAN
(in Annex 2. Supplementary Information- 3.1.4: Corrective Actions Following The Mid-Term Evaluation)

A supplementary comment came from The "Steering Committee (CoPIL)". **The CoPIL asked FBI to show that the financed projects "aimed for a high level of mutualization and integration".**

Our goal is of course to serve a wide scientific community in such a way as to enable it to obtain the best results, to carry out its studies successfully and to gain visibility, thanks to a technological service and expertise at the highest level. This seemed to us compatible with the definition of the primary missions of a Research Infrastructure and we show that this strategy was not unsuccessful (**See again Annex 2 Supplementary Information-3.1.4: Corrective Actions following the mid-term evaluation**)

3.1.5: PRINCIPAUX FAITS MARQUANTS ET LISTE DES 20 PRINCIPALES PUBLICATIONS / MAIN HIGHLIGHTS AND LIST OF THE 20 MOST RELEVANT PUBLICATIONS.

STRICTLY IN THE ACKNOWLEDGEMENTS SECTIONS

From users (co authorship by FBI members in Bold ; inter-FBI nodes collaborations at the end)

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4. Matthieu Pierre Platre, Vincent Bayle, Laia Armengot, Joseph Bareille, Maria Marques-Bueno, Audrey Creff, Lilly Maneta-Peyret, **Jean-Bernard Fiche**, **Marcelo Nollmann**, Christine Miège, **Patrick Moreau**, Alexandre Martinière and Yvon Jaillais Developmental control of plant Rho GTPase nano-organization by the lipid phosphatidylserine. ***Science***, 2019, in press. (***inter nodes***)
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From FBI members Team and Core F (in Bold)

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3.1.6: INDICATEURS CHIFFRÉS DEMONSTRANT LA PLUS-VALUE DE L'INFRASTRUCTURE / NUMERICAL INDICATORS DEMONSTRATING THE ADDED VALUE OF THE INFRASTRUCTURE.

*Here are presented significant numbers for only five indicators. An extended and **detailed IMPACT STUDY** is presented in **Annex 2. Supplementary Information. IMPACT STUDY***

1) Number and impact of publications in international journals¹

Briefly Under WoS (strict thanks only in the "**Acknowledgements**" section, according to our charter)

SEARCH: FUNDING AGENCY: (france bioimaging) OR FUNDING AGENCY: (francebioimaging) OR GRANT NUMBER: (ANR-10-INBS-04-) OR GRANT NUMBER: (ANR-10-INSB-04-)

Total Publications= 601 as for the 19.03.2019 (2013=19; 2018=154); Number of citations (without self-citations) = 8114 (2013=44; 2018=3235) Global H-index =38 (average number of citations per publication= 14.37) Average journal IF of all publications at 5 years in 2018 = 9. Average IF of user publications at 5 years in 2018= **9,3** (possible co-signing RI members, but not main authors)

2) User access and beneficiary institutions. Between 2012 and 2018, **from 1768 to 4658 users** (including users of software Platforms, and the recently created Image Analysis Hub@Institut Pasteur) for an estimated doubling of projects (approximately **2000 projects in process** in 2017 compared to **1200 declared** in 2012). We also monitor the level of FBI impact for our Research Institutions (CNRS, Inserm, Univ, Institutes...) by quantifying the *Number of Reviews co-citing FBI and Research Institutions indicated (more than 88% indicate CNRS)*

3) Analysis of projects; "processed" or "completed"? "**Projects Declared By Nodes**" in 2012=1200; referenced as "**Completed Projects**" In 2016= 1920, 2017= 2084, 2018= 2405

Technological Occupancy Rate 75 to 80% (for a total capacity up to 85%)

Human Resources Occupancy rate 100% (with increasing activity from Engineers on short term contracts)

Average Waiting Time before project processing = **15 days** (with very large deviation depending on the sophistication of the approach)

Analysis of "success/completed projects" Measured by *conventional "key performance indicators"* (publications, patents, operating licences, PoC, Soleau envelopes, APP filing numbers, theses, etc.).

An approach using "**Full Text**" search (**Google Scholar**) modalities gives, **395 projects were "completed"** in 2017. More reasonable is the collected number by the **National Coordination (around 250)**

*For identification of "Successful projects", involving or run by users outside the regional scope of FBI nodes (Trans Access), see **Annex supplementary Information**.*

¹ It should be noted that another search using "Google Scholar" for "france-bioImaging" or "Francebioimaging" which would include **acknowledgements** in "**mat and meth**" sections gives a number of publications =**1160**

4) Impact Education and Training. FBI offers quality local educational training (participation in more than 40 to 50 programs/year (M1/M2, 6 ED programs,...), with strong specializations, depending on the Nodes and Sites and the audiences concerned. FBI participated in the organization of 50 to 60 continuing education courses with national and international institutions (CNRS, CNRS entreprises, Inserm, EMBO, IBMC (Portugal), I3S (Spain), EMBS Summer School) or as part of international programs (Global BioImaging; RetUBI; EuBIAS and NeuBIAS; FENS-Neurosciences School of Bordeaux). FBI was the leader of WP Training in EuroBioImaging-ERIC's PP11, organized the first workshop on "Core F staff Training-EuBI" in MIFOBIO-2016 and the first international symposium "Next Generation Training In Biological Imaging" during the Focus On Microscopy, Congress in 2017. FBI develops its own training actions, when the need is not covered elsewhere. Finally, about **1500-2000 users/year** are trained on sites by our expert platform operators. **Identified needs** are: readable communication of the offer; development of an advanced training program and the construction of a training plan with validation/certification; reinforcing the professionalization of platform staff; the development of training courses concerning advanced or emerging techniques, progressive and at different levels depending on the audience (from information to practical workshops); the development of training courses dedicated to the analysis and management of image data. Our training plan is established in consultation with training stakeholders (training departments, business networks, Industrial Committee...) (see section **3.2.5 TRAINING**).

5) Contract financing. FBI finances an increasing part of its needs through significant successes in various tenders and is in a position to cover **about one third of its budget needs** per year (which Total can be established between 25 and 30 M€). However, this might be submitted to fluctuation from one year to the other, those calls are mostly devoted to R&D "projects" and "new equipment acquisition" and rarely for running and employment costs. For all types of contracts (both academics and private contracts; Foundations, Regional, National and International Calls; not included **other PIA funding**), from **3.3 M €** in 2014 up to **11.6 M€** in 2018 (from which about 1.6 M€ are provisions to be spent in 2019) (see also section **3.3.4: MEANS PROVIDED THROUGH CO-FINANCING**.)

3.2. IMPACT SOCIO-ECONOMIQUE / SOCIO-ECONOMIC IMPACT

3.2.1: RETOMBEES POUR LA COMMUNAUTE SCIENTIFIQUE / IMPACT FOR THE SCIENTIFIC COMMUNITY.

"Impacts of RI-FBI" on the scientific community, on Research Institutions, both partners or outside the FBI scope, as well as on visibility via "international collaborations of national teams " are detailed in the **Annex 2. Supplementary Information. IMPACT STUDY**. The table below summarizes the impact of the RI FBI by comparing two scenarii. Some elements (in grey) are still indicated as actual and next priorities.

ADDED VALUE OF THE FBI-INBS NOW AND BEYOND

SCENARIO	WITHOUT FBI	WITH FBI
Infrastructure	Isolated, standard commercial technologies, poor progress	State of the art equipment, serviced, available on demand, organised
	"Privately" owned by single research labs; Risk of poor usage at short term	Pooling of resources and shared expertise
	Institutes mostly offering access to in-house researchers	FBI available to external users. Collaboration, visibility, attractiveness...the "2" market model?
Service provision	Service protocols dominated by local practices	Integrated, quality-assured, integrated workflows, and coordinated, unique and advanced services.
Costs	Under-utilised platforms leading to higher access cost	Platforms optimally utilised keeping costs of access low
	Risk for the core Facilities to operate at loss	RI can operate closer to FEC
Innovation and industrial liaison CONCEPT FOR TECH. TRANSFER	Limited ability to respond to industry needs.	Trained staff, networked liaison officers, strategy for innovation, wider ability to provide solutions
Scientific impact	Low dissemination and knowledge transfer, limited access to High End "technology"	Joint-up capabilities, adoption of a culture of excellence; Deliver a broader scientific impact than the sum of the operator could achieve
Data collection	According to local practices	Definition of Standard Operation Procedures Harmonization of data collection practices
	Fragmentation of repositories	Gold standard practices with networked resource
	Low or no data interoperability Lack of visibility and loss of the data collected	High probability of Inter-operability Secured and High visibility of data for the research and industrial community

3.2.2: IMPACT POUR LA DECISION PUBLIQUE / IMPACT FOR PUBLIC DECISION-MAKING.²

FBI is a research infrastructure whose primary objective is scientific excellence. In this sense, at least with regard to its R&D activities and services towards the academic world, it is essential that it can rely on public resources dedicated to the acquisition of knowledge. The measurement of its "socio-economic" impacts must be different from the traditional techniques and tools used in other sectors. However, it will be noted the importance that the PIA INBS program has had and will have on the training of young engineers and doctors, the coherence and rationalization of the proposed service and the implementation of practices to guarantee its quality and professionalism. Technological and methodological transfers from the RI FBI to the socio-economic world, have evident impacts in the fields of diagnostic analysis, the design of new drugs, environmental impacts on biodiversity and its development, and the creation of alternative methods to animal experimentations. Moreover, FBI RI long term impact on the emergence of and employment in new innovative economic sectors, started to appear in 2017-2018. This should deserve the consideration for another 5 to 10 years before to be objectively measured (*See Sections 3.2.4 and 3.3.3 Impact In the Socio-Economical Sector*).

² On this aspect, the RI FBI National Coordination, participated in the PIPAME report "Medical Imaging of the Future" in 2013.

3.2.3: PRINCIPAUX BREVETS ET LICENCES, EXPERTISES REALISEES / MAIN PATENTS AND LICENCES, EXPERT EVALUATIONS PERFORMED.³

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8. Fluorogen Activating and Shifting Tag (FAST), A. Gautier, L. Jullien, International Application No.: PCT/EP2015/065267 **Led to the foundation of the startup Twinkle Bioscience in May 2017;**
9. Method for the detection of reversibly photoconvertible fluorescent species, V. Croquette, A. Gautier, L. Jullien, T. Le Saux, S. S. Nath, J. Quérard, P. Wang., International Application No.: PCT/EP2014/075336
10. **Since 2011 UTechS PBI** (Pasteur) : (1). EiPE (Enzyme-independent photon emission): EP14/305509.3 07/04/2014, PCT/IB2015/052495 07/04/2015

3.2.4: PARTENARIAT AVEC LES ENTREPRISES ET RELATIONS CONTRACTUELLES ETABLIES / INDUSTRIAL PARTNERSHIPS AND CONTRACTUAL COLLABORATIONS ESTABLISHED.

Industrial Use and Partnership

FBI's marginal financial investment in R&D through the PIA funding is largely responsible for our international visibility and has largely contributed to increasing the level of the infrastructure outreach in the private sector over the past 5 years (joint public/private international publications, copyrights, operating licences, etc.). Pharm or biotechnology companies (Sanofi, Servier, OGD2-pharma, ABIVAX...) and cosmetics companies (L'Oreal, Clarins...) are "users" of FBI, sometimes in a "service" mode but more often **under contractual terms**.

But the impact of FBI is manifested in the economic world, especially by,

1) links with French small companies, which develop innovative systems, that we support (BioAxial, Imagine Optics, Fluigent, Innopsys, BioEmergences-PhaseView- construction of a joint laboratory - **ANR-LabCom**) and with which FBI has developed original partnerships. Some have their "roots" or have been created during the FBI-PIA such as *Alveole*, *Obsys Scientific*, *CryoCapCell*, *GATACA Systems* (created in 2017), *Twinkle* (created in 2017), *Quantacell*, *Karthala System* (created in 2017), startup

³ Note: we cannot provide here an exhaustive or even select a list of FBI member participation to Expertise in the field of Biolmaging (IBISA, ANR, BPI, EC, EMBO, Foreign Funding Agencies, drafting of technical files, member of SAB and Steering committees, project evaluation...). This would exceed 100 elements per Year.

being created around the soSPIM project in Bordeaux (to be created in 2019), and the visualization of scientific data in virtual reality (*DIVA*, as part of an agreement between Institut Curie and Institut Pasteur). Most of them are Members of our **Industrial Committee**.

2) the success of software developed during the project (nD-Safir, denoising software integrated in the Metamorph suite before FBI and in the ProEM 95B Roper/Photometrics camera in 2017; WaveTracer software with Molecular Device; eC-CLEM and HPM-fast with CryoCapCell, Nikon and probably Zeiss. in the future..)

3) finally, most FBI Nodes maintain **privileged contractual relationships** with major companies in the field. Our strategy to **offer “open premises”** for common developments and β -testing opened “win-win” collaborative engagements with Nikon, Leica, Zeiss, Roper Scientific/Photometrics, GE Healthcare, Technicolor, 3i, Brucker, Konica Minolta.

3.2.5: FORMATION / TRAINING.

As previously mentioned, FBI is involved in user and core facility staff training and initial training both at the national and international level. FBI, through its core facilities and R&D teams, brings together a distributed quality training offer, with strong specialization areas matching Technologies and Scientific topics, according to the Nodes. Within its full scope, FBI welcomes and trains **about 1500** new users per year (1800 in 2018). Experience shows that face to face learning and hands-on training cannot be replaced when it comes to ensuring that users acquire the required “know-how”. The success of these practical training therefore depends on instructors, in this case **core facility staff**, who must be optimally trained themselves. Every year, the FBI training portfolio includes participations and co-organisations of courses in Licence and Master programs (44 in 2018), including Master programs dedicated to imaging core facility staff training in two universities, and participation or co-organisation of doctoral programs including international PhD programs (5 in 2018) and engineering schools - Grandes Ecoles, Mines, ESPCI, ENSAI, Ecole Centrale- (11 in 2018). Moreover, FBI participates in the organization of lifelong training courses (55-60 in 2018) with national and international institutions (CNRS, CNRS Formation Entreprises, Inserm, INRA, Institut Pasteur, Institut Curie, EMBL, EMBO, IBMC (Portugal), I3S (Spain) Gulbekian Institute (Portugal), Imperial College (London), EMBS Summer School) or with other European and international programs (ELMI, Global BioImaging.INFRADEV H2020; RetUBI Twin H2020; NeuBIAS Cost Action; FENS-Neurosciences School of Bordeaux).

Since 2012, FBI is highly involved in dissemination activities in biological imaging, in particular through the organization or co-organization in France of major international congresses (ELMI, FOM, QBI...). It is worth adding here the CNRS MiFoBio thematic school, where FBI core facility staff and associated R&D teams are key participants, and whose international aura acquired today is due in part to the support and promotion of FBI. Also, FBI supports every year, internal training activities organized by the national imaging community Networks (RTmfm, RCCM) and participates in networking actions for imaging core facility staff.

Beyond its active role as participant and support for training activities for the imaging community, FBI is also convinced of the importance to build a more integrated training offer to ensure there is sufficient biological imaging capability in France with opportunities for training at all levels, and sustainable career pathways. The future of biological imaging is reliant not just on technologies but

on a well-trained and highly skilled community of developers, users and core facility staff. As such, high-quality training should be well supported by all stakeholders. That is why FBI has set up a FBI Training Service in 2018 with the aim to be proactive in the construction of a “training passport” for biological imaging. This “**training passport**” (See **ANNEX supplementary information-TRAINING**) should not be limited to biology PhD students but spans across disciplines and all career stages. The technology/methods development and the use of biological imaging require different levels of cross-disciplinary knowledge and expertise, including image analysis. Finally, training can be supported through various mechanisms but available training and skills resources must be well advertised and accessible to the whole community, hence the importance for FBI to develop a training portfolio on its new website (**in progress**) available for the French biological imaging community but also for the international community and stakeholders.

3.3. MOYENS MIS EN PLACE / IMPLEMENTATION

3.3.1: ORGANISATION ET GOUVERNANCE / ORGANISATION AND GOVERNANCE.

FBI Governance plan starting in 2019 and prospective for 2020-2025 - Operate and Evolve

The FBI governance is structured around a Director and an Executive Board (EB), supported by the National Coordination staff (within the **UMS 3714 “CeMiBIO” in 2019, since 2015**). The Director of FBI is the UMS Scientific Director. Altogether, this is the body for the implementation of FBI’s overall strategy defined with and approved by the Institutional Committee. This scheme has been defined after some modifications and explanations by the coPIL of the Research Infrastructures (In 2018).

The strategy, management and operation of the infrastructure are also supported by the advices of an International Scientific Advisory Board and a National Scientific Council composed of 3 sub-committees (*Technology Watch Committee, Users Committee and Industrial Committee*).

The overall architecture of FBI governance with the strategic and operational levels is summarized in the organizational chart (**in the section 4.4.1: Expected changes in the governance structures**), with some ongoing implementations and additional strategic elements which we propose for the future. The corresponding components of the FBI’s governance structure are detailed below.

Strategic Management

Institutional Committee (Steering Committee):

This is the decision-making committee supervising and approving the overall strategy of the infrastructure, its major axes of activities and the proposed evolutions in the perimeter of the infrastructure.

Executive Committee or Board (EB)

Its main role is to translate the FBI's overall strategy, defined with and approved by the Institutional Committee, into operational actions.

The EB is composed of the National Coordination of FBI (Director, Administrative and Financial Manager supported by an Administrative and Financial Assistant, a Manager for Europe/International activities, Mission Officers and a Communication Officer) + FBI Nodes Coordinators. Meetings are organized once a month. Two representatives of the FBI Core Facility Staff Working Group (engineers

of the infrastructure platforms, see below) are invited to the EB meetings and can participate to the decisions.

International Scientific Advisory Board (SAB):

Prospective, scientific and technological advices on the infrastructure activities, and advices on potential changes to the infrastructure perimeter. Meeting before or during the FBI Annual Meeting (1 per two-years); renewal of member(s) according to expertise and infrastructure needs.⁴

National Scientific Council:

The EB of FBI also relies on the advice of a National Scientific Council composed of the following 3 committees:

- **Technology Watch Committee:** composed of representatives of the RCCM and RTmfm networks, and technological research groups (such as GDR IMABIO) in our field. Partnership agreements have been signed between FBI and the RCCM and RTmfm networks.

- **Users Committee:** composed of external users (located outside the FBI perimeter) of our facilities⁵ It provides independent recommendations/suggestions on the activities of FBI users. It completes the Node User committees (**or Node Community**; users located in the regional perimeters of FBI Nodes)

- **Industrial Committee:** composed of representatives of companies involved in the field of microscopy (French start-ups to large companies in equilibrated weight). It is actually composed of: *Abbelight, Alveole lab, Amplitude-systems, Bioaxial, Cryocapcell, Gataca-systems, GE Healthcare, Imagine-Optic, Twinkle Biosciences, Leica-microsystems, Nikon, PhaseView, Quantacell, Roper Scientific-Gatan, Thermofischer and Zeiss.*

Representatives of these Committees are invited to the monthly EB meetings, depending on the topics discussed. They have an advisory role on decisions of the EB.

Annual plenary meeting of the National Scientific Council at the "FBI Annual Meeting" + 1 meeting / year National Coordination with representatives of External Users. Extraordinary meetings with either of these committees, on focused topics, are organized as needed.

⁴ In 2017-2018, the members of the SAB were **Enrico Gratton** (SAB President, Professor of Biomedical Engineering and Physics, University of California, Spectroscopy / Biological Imaging), **Luis Bagatolli** (Professor, University of Southern Denmark), **Teng-Leong Chew** (Director for the Advanced Imaging Center, Janelia-Howard Hughes Medical Institute, Light Microscopy), **Francesco Pavone** (Professor, University of Florence, Biophotonics Microscopy / Neurology), **Carolina Wählby** (Uppsala University, Quantitative Microscopy), **Yannick Schwab** (Head of Electron Microscopy Core Facility, EMBL), **Markus Sauer** (Chair of Biotechnology & Biophysics Biocenter, University of Würzburg)

⁵ (List of representatives in 2018: **For Bordeaux** :Dirk Schaumlöffel (Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement et les Matériaux (IPREM) UMR 5254 / LCABIE, Université de Pau) ; Harald Wodrich (Laboratoire de Microbiologie Fondamentale et Pathogénicité UMR-CNRS 5234, Inserm, Bordeaux). **For Ile de France Sud** : Laure Crabbé (Université Paris-Saclay). **For Marseille** : Emmanuelle Renard (Institut Méditerranéen de Biodiversité et d'Ecologie marine et continentale, IMBE UMR 7263, Marseille) ; Lionel Berthaux (UMR 7256 Information Génomique et Structurale, Marseille) ; Jenifer Croce (Observatoire de Villefranche-sur-Mer). **For Montpellier** : Silvia Zorrilla (Consejo Superior de Investigaciones Científicas, CSIC, Madrid) ; Jean-Yves Bouet (Centre de Biologie Intégrative de Toulouse). **For Paris-Centre** : Jennifer Gommerman (University of Toronto) ; Guillaume Pidoux (Inserm/Paris-Saclay/Chatenay Malabry) ; Sandra Piquet (UMR7216 CNRS Université Paris Diderot) ; Nicolas Chevalier (Matière et Systèmes Complexes, Université Paris Diderot) ; Guillaume van Niel (Centre de Psychiatrie et Neurosciences, U-894 INSERM).

Operational Management

National Coordination (In 2019 Coordination is supported by the UMS 3714 Created in 2015; it is constituted of the personnels indicated below)

Appointments/Recruitments

- The appointment of the Director is proposed by the EB to the Institutional Committee which validates the appointment. The EB, on justified grounds, may request the dismissal of the Director and initiate the procedure for the appointment of a new Director.
- On proposal from the Director and/or the EB, the Mission Officers are appointed by the Director in consultation with the EB.
- The Administrative and Financial Manager is recruited by the Director in agreement with the EB according to the assessments of the candidates carried out by the National Coordination.
- The Communication Officer and the Administrative and Financial Assistant are recruited by the Director in consultation with the National Coordination.

Mode of operation of the Director's and EB's decisions

The majority of operational decisions about the operation of the infrastructure are made by the Director in concert with the EB at the monthly meetings. In cases where a collective consensual decision of the EB cannot be reached, there is a vote. Each node has one voice. In case of equality, the decision is taken by the Director.

Director of the infrastructure:

Infrastructure management with the Institutional Committee, the SAB and the EB.

- Responsible, following recommendations from the EB, for the arbitration of the recruitment proposals (national coordination, nodes), equipment investments (PIA, TGIR...) in relation to the development objectives (R&D, service offers...) and the overall infrastructure development policy at national and international level.
- Responsible, with the staff concerned, for the inventory of the different activities/tasks of the infrastructure: links with Europe and International, work with the different committees (see below), web site/communication, trainings, animation of the community, scientific and financial reports...
- Responsible, in interaction with the EB, for managing interactions/collaborations (R&D, service providing, partnerships, technology watch...) with other PIA Research Infrastructures.

Administrative and Financial Manager (IR level):

- Steering and management, in coordination with the Director and the EB, of all organizational matters.
- Responsible, in interaction with the Director and the EB, for the administrative/financial monitoring of the infrastructure's operation in relation to the various administrations and financial managers of the infrastructure nodes, supported by an administrative assistant.
- Responsible for the implementation of the policy of promotion of the infrastructure with the scientific community and the academic and industrial partners.

- In support to the Director and the EB to make a return on the activities of FBI to the Institutional Committee with a regular frequency to be defined (1 to 2 per year) to give them a visibility and a follow-up on FBI activities and achievements.

Administrative and Financial Assistant (AI level): *(See also perspective of sustainability. 4.4.1: Expected changes in the gouvernance structures)*

An Administrative and Financial Assistant position is requested to assist the Administrative and Financial Manager (coordination funds, management of funds from other sources, auditing information, ERIC-EuBI transnational access...).

Manager for Europe/International Affairs:

- Representative of the French Node (FBI) at the executive committee of the ERIC EuBI (European Infrastructure for Biological and Medical Imaging).
- Responsible for the various interactions to be developed with the European (EuBI; ELMI...) and International (Global BioImaging; CTLS association; ...) imaging communities.

Communication Officer:

- Coordinates FBI communication via the website and social networks, edits other communication tools (newsletter, flyers, stickers, FBI booth...) and assists the National Coordination, its Mission Officers and the Nodes in all their outreaching activities including all regional, national or international event organized or co-organized by FBI.

3.3.2: MODALITÉS D'ACCES ET TARIFICATION / ACCESS MODE AND PRICING STRATEGY.

Access Mode.

A number of elements concerning "Access and Project" processes are already mentioned in different part of this document (and part of our Performances Indicators). Here we will summarize the diverse modalities. We can define three different modes of Access, although at the end the support procedures are identical on all sites.

1) Through direct local contacts, hopefully via e-management systems. Good news, today most of the Users are contacting platforms through professional e-management and booking systems (Stratocore-initially developed by the Head of the imaging core facility at Pasteur Institute, the Ilab Solution and the OpenImaris collaborative solution, to which FBI-PICT, FBI-IMACHEM in Paris and PicSL in Marseille, collaborate). Unfortunately, we still did not convince all of the 11 FBI CoreF manager about using a single system.

2) Through the FBI Web Access Portal in the "Call for Project". This portal is more devoted to users who do not know where to address their questioning and often what kind of expertise they need. This constitutes our "second circle of Users". This procedure is unfortunately marginal and do not exceed a few dozen of project per year. On the other hand, this worked for international colleagues and provided some visibility and collaborative studies over the past year.

3) At the European level (see international strategy), we will open our offer through the EuBI-WAP. A “pilot WAP” was proposed over the EuBI-preparatory phases. A question in the near future is how to match this EuBI-WAP with our national one (in progress).

Pricing Strategy.

Thanks to the full cost operation launched by the DGRI-MESRI in 2016, we have now a clearer view of the global cost of FBI services and operations. We can estimate a pricing list depending on the nature of service offer and the type of technologies to be used. Here is presented a summarized table, with averaged costs for academics users, using “Hours.Machine.Human” as a **Unit Cost** (full cost, minus amortization and new investment). Other models are possible (as Project unit Cost; Days of Access Unit Cost....), which could be more adapted to some provided services (HCS projects, CryoEM...).

FBI ACCESS	Hours	Access. Hours	Regular LM	High End Confocals (2P, FCS, FLIM...)	High and SuPerRES	Lattice Light Sheet	Longitudinal Intravital	Regular EM/TEM	High end EM-CLEM/Tomo-CryoEM/FIB-SEM/SBF	TOTAL CTL Hours
E. Total quantity of access provided to academic users of the installation (i.e. both internal and external) over the last two years ^[3]		624 800	499840	21868	20618	20618	20618	20618	20618	624800
F. Unit cost =D/E		42,75 €	28,72 €	45,29 €	46,22 €	80,19 €	80,17 €	90,60 €	112,60 €	

For industrial Users, full cost would mean these “F.Unit.Cost”+ equipment amortization+20%. However, in most places the use of our Core F by Industrials is driven **by valuation local services, which have their own modalities and strategies.** Finally, we still wait for **Institutional Organizations** (CNRS, Inserm, UNIV, Semi-Private/fondation Research Institutes...) **to agree on a common “Pricing Strategy”** at the national Level.

3.3.3: MOYENS HUMAINS ET FINANCIERS SUPPLEMENTAIRES APPORTES PAR LES PARTENAIRES DEPUIS LA CREATION DE L'INFRASTRUCTURE. / ADDITIONAL HUMAN AND FINANCIAL RESSOURCES PROVIDED BY THE PARTNERS SINCE THE CREATION OF THE INFRASTRCTURE.

Additional financial resources directly provided by Institutional partners during 2012-2018

Before 2015 we are unable to detail the monetary resources provided by our 13 institutional partners. Instead we provide here the **average resources/year** based on the last 4 years (2015-2018). The main contributors are, **Institut Pasteur 1.4 M€; CNRS 0.4 M€; Institut Curie 3.0 M€; P5+P7 (UP) 0.15 M€; Inserm 0.04 M€; Inria, 0.03 M€; BU 0.02 M€; ENS 0.015 M€; SU 0.017 M€**

It should be noted that these numbers do not take into account the infrastructure costs which have been estimated in the frame of “the full cost operation” organized by the Ministry of Research, only for 2016 and 2017. Labex, other PIA funding and Internal Calls, piloted by these institutions are also excluded.

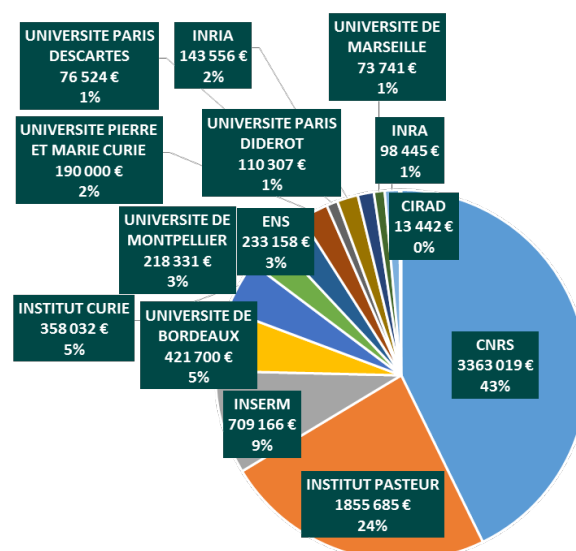
*The analysis below does not distinguish between positions on fixed term contracts and permanent posts. (See also Annex 2. Supplementary Information. For detailed **additional resources provided by the partners**)*

Additional open positions during 2012-2018, CNRS 6 Research Engineers (IR), 5 Study Engineers (IE); Institut Pasteur 4 IRs, 2 T (technicians); Inserm 3 IRs; AMU 1IR, 1 IE; Univ Paris Diderot, 1AI (Assistant Engineer) , 1IE; Ecole Polytech/MORPHOSCOPE, 1 MCU (Assistant Professor), 1 IR, 1 T; Institut Curie 1 IR (IT dept, start in 2019), 1IR (Labex/PSL) ; Paris Sud (PARIS SACLAY) 1 IR ; UB, 1 IE ; Probably 1 IE from MU (?)

Lost in Human Resources during 2012-2018, CNRS 8,8 IR, 4 IE; Institut Pasteur 3 IR, 1 IE,1 CR (Researcher); Inserm 1 IE; AMU 1 IE; BU 1 T.

Comments. Despite differences in the level of recruitments the balance is positive **with about 10 supplementary positions and a broader diversity of the institutional partners that provided the human resources.** However some disequilibrium between Paris-Ile De France and the other Nodes in Regions appears. Moreover, **this analysis does not distinguish between positions on fixed Term contracts and permanent posts.**

In order to give a clearer view on which Institutional partners (sometimes not part of the Consortium Agreement) participate to the FBI Human Resources, we also provide the following diagram of the **Average of human cost/year for permanent positions.per Partners calculated for 2016 & 2017**



3.3.4: MOYENS APPORTÉS PAR DES COFINANCEMENTS / MEANS PROVIDED THROUGH CO-FINANCING.

For the sake of space, we cannot list all sources of co-financing in this document. We simply provide here a table that compiles the total amounts obtained and used the last 4 years, which correspond to **a full regime of the RI FBI operation.** We also indicate the % of total FBI resources (including Human

Resources but excluding **funding via the program PIA-INBS** (ANR-10-INBS-04)) this co-financing represents,

YEARS	2015	2016	2017	2018
Total in €	6 893 320,00	7 813 200,78	7 759 268,40	10 046 099,00
% of Ressources	28	33	31	40

A list, with indicated origins of these co-financing, for these last four years is *provided in Annex 2. Supplementary Information*. It should be noted that although the RI FBI was particularly successful in this funding aspect at all levels (Regional, National and International), thanks to the lever effect induced by the PIA program, this remains time consuming and exceptional financing, as some fluctuations over the years demonstrated and may appear in the next years. It makes the RI strategy submitted to instability and clear allocation uncertain. Yet, we optimistically believe that this part of our budget should be stabilized around **one third of the total resources** in the future.

4. PROJET POUR LA PERIODE 2020-2024 / PROJECT FOR THE 2020-2024 PERIOD

4.1. PRESENTATION SYNTHETIQUE DES ARGUMENTS POUR UNE PERENNISATION DE L'INFRASTRUCTURE/ SYNTHETIC PRESENTATION OF THE ARGUMENTS FOR THE LONGER TERM CONTINUATION OF THE INFRASTRUCTURE.

A first series of arguments which compare two scenarri is provided in Section: 3.2.1: IMPACT FOR THE SCIENTIFIC COMMUNITY.

The scientific objectives of the FBI-Next Generation project is to invent and provide the biological imaging technologies of the future and to ensure the sustainability of the data produced. The technologies previously developed within the FBI have already had a major impact on the scientific and societal challenges of Life Sciences (fundamental mechanisms in cell biology and development, host-pathogen interaction, stem cell biology and regenerative medicine, plant physiology, study of marine organisms and their development in a constrained environment, cancer, neuroscience and degenerative diseases...).

-The need for an assumed integration of the infrastructure in a long term continuation is justified by the coordinated and multi-site projects proposed in the next sub-section 4.2.1: NEW DEVELOPMENTS JUSTIFIED BY SCIENTIFIC AND TECHNICAL EVOLUTIONS.

The objectives will be to:

- 1) strengthen the consideration of the needs of various types of users (academic, industrial and societal) to identify new markets,
- 2) capitalize on the synergy between infrastructure nodes/sites and with coordination,
- 3) establish and re-evaluate continuously an economic strategy based on the integration of projects proposed by the different parties constituting the infrastructure,
- 4) build/program the availability of developed technologies, to other non-FBI sites or other National Infrastructures, which can provide complementary expertise.

- The FBI is the only national structure that can draw and lead a **roadmap for biological imaging with economic and business models for the next 5 to 10 years** provided it can stabilize the necessary

human resources in administrative support (report "**Roadmap for National BioImaging**" provided to IBISA, in July 2018),

-The main ambition of the "**Next Generation FBI**" is to integrate the technologies and methods previously developed within the FBI, by coordinating 6 areas: Multi-/Trans-Scales, Multi-Modes, Integration, Miniaturization, Automation, High Content/High Throughput Screening. This ambition is accompanied by an increase in the means of analysis, processing and management of massive "image" data.

-Each component of the FBI, individually, is not in a position to gather and disseminate the necessary innovations. Only coordination by the FBI, combined with careful monitoring of the evolution of its scope and expertise, will enable France to remain at the forefront of life imaging in Europe and abroad, in line with the training in these technologies, the renewal of a relevant national industrial sector in this field, which we are supporting and developing. "**Innovation-Training-Access**" will definitely remain our motto.

4.2. PRINCIPALES EVOLUTIONS ENVISAGEES / MAIN PLANNED EVOLUTIONS

4.2.1: NOUVEAUX DEVELOPPEMENTS JUSTIFIES PAR DES AVANCEES SCIENTIFIQUES ET TECHNOLOGIQUES / NEW DEVELOPMENTS JUSTIFIED BY SCIENTIFIC AND TECHNICAL EVOLUTIONS.

*The rational and elements of Development of the **Next Generation-FBI project** adjusted from the previous years (2017-2018) Is presented in details in the **Annex 4-FBI Next Generation, PIA3-2018 version.***

It is necessary to consider the new fields of application of our current users and the extension of FBI's scope of activity to new target users. The four topics briefly described below are the results of a broad concertation with User committees (both external users and local user committees), all the Core F staff at Nodes (now, with the new **FBI Core F WG**), some outreach discussions at the European and international level (concerning Emerging technologies in the scope of the EuroBioimaging and Global BioImaging projects) and our Tech Watch Committee. We also consulted some of our industrial partners (for instance, ThermoFisher, GE Healthcare, Servier and ABIVAX).The main technological lines are,

(1) The deployment of combined imaging modalities (SR-3D, LLSM and Live-Correlative Microscopy...) for the visualization of biological structures at the nano, micro and mesoscopic levels, in their cellular context, coupled with measurements of their dynamics and interactions.

(2) The integration of new imaging technologies deployed or developed within the FBI (Super-Res and Unique Molecules, fast-3D Unique and Multicellular Cells) with automated instruments for high throughput phenotypic screening (HCS) analysis.

(3) A sustained and streamlined effort in the processing and management of Bbio-Image data through the creation of **the FBI-Image Analysis Service**, in the perspective of a necessary syncretism, with the new phenotypic and -omics data is clearly a challenge that exceeds the only FBI perimeter (project to be developed in Inter-IR interaction of the PIA).

(4) Continue the development of contrast agents, related to the emergence of photo-intervention and optogenetic techniques (from cell to in vivo on small animals).

If we analyze the service provided by FBI, we have to admit that in a first step, the PIA funding was largely used for the replacement of regular light microscopy setup (wide field and confocals) that were already present in the single platforms and offered to restricted user perimeters, in up-to-date equivalent systems that provided innovative approaches on top of the same modalities (confocals with STED; wide-field with PA/FRAP/FRET module or TIRFM with STORM/PALM) .

As already stated, FBI responses and added value for the user communities are now more and more orientated to demand when “local services in imaging”, due to their limited equipment, expertise or availability, can no longer do so. More precisely and as our statistics indicate, the FBI intervenes specifically, when the equation "bouquet of technologies/expertises/thematic environments" is no longer solved. Thus the installations, expertise and new services foreseen and proposed in our **“Next Generation FBI” project (See Annex 4-FBI Next generation, PIA3-2018)**, for the next 5 to 6 years, are clearly based on this philosophy. We do not deny however, that due to the specificity of regional scientific topics and the local scope of users, each FBI core F, will need to maintain at the best level of quality, regular advanced technologies which serves Users in their “Day to Day” research.

4.2.2: CHANGEMENT DU PERIMETRE ET SERVICES PROPOSES EN FONCTION DES AVANCEES SCIENTIFIQUES ET TECHNIQUES OU DES BESOINS DES UTILISATEURS / CHANGES IN SCOPE AND IN SERVICES OFFERED DUE TO SCIENTIFIC AND TECHNICAL EVOLUTIONS OR USER NEEDS.

Criteria and modalities for entering and leaving the infrastructure perimeter

FBI was built on the concept of Nodes where a high quality service offer to a wide range of users is linked to the development of new approaches in Bioluminescence. These developments are carried out by **associated R&D team in the strict perspective of technological transfer to facilities** or by the central facilities themselves. For these Core Facilities, **the strict fulfilment of the IBISA criteria and therefore the IBISA label are prerequisites**. This is what our motto "innovation-training-access" defines. In this regard, each node and eventually sites, must demonstrate its ability to implement a technology transfer assessment process, if possible beyond local/regional accessibility. The combination of innovative imaging platforms and laboratories has made it possible to accelerate the implementation of these innovations, according to users' needs. **Beyond these criteria, the FBI's distributed infrastructure is based on a match between a technological offer and a specific user pool**. Each Node has and must have an identity that lies in the cross-fertilization between technologies, sometimes identical, and expertise on the one hand, and the expectations of particular user communities (neurosciences on the Bordeaux Node; chromatin structure and genetic regulation in Montpellier; fundamental immunology in Marseille; Plant cell biology in Paris Sud; host-pathogen and cancer research in Paris.....).

These are the **main criteria which needs to be evaluated** for any changes in the FBI scope. In consequence,

R&D Teams or Laboratories that would not show their link to core Facilities and demonstrate their capacity to transfer their innovation to users, **should leave the FBI scope**. FBI through consultation of Users needs and its “Tech Watch committee”, and in a continuous search **for New User communities**, will seek after **New R&D labs and teams** to develop **New Projects**. These projects should be considered with flexibility as fixed term projects (duration to be evaluated). This would define **the entering criteria of FBI Associated R&D labs (or Core Facilities), in the future**.

Imaging Core Facilities that would not answer the strict IBISA criteria on access modalities and running procedures or that would not advertise on their IR FBI belonging **should leave the FBI scope**.

Any institutions that do not provide and declare any support to the IR FBI should leave the IR perimeter and consequently **should not sit on the Institutional Committee** (future Steering Committee).

For all changes (leaving and entering) beyond an internal closing or opening of “Particular Service” or “Technological Access” on operating Nodes, the evaluation process would have to be discussed, but should follow the,

Five steps modality we used in 2017 for our call on **“Declaration of Interest TO JOIN THE INFRASTRUCTURE”** and described in *Annex 2 Supplementary Information-4.2.2*.

We will extend this evaluation process (every three/four years) to both the “actual scope of each operating Nodes” and for the opportunity to recruit among “New node Candidates”. A 6th step is necessary, which unfortunately never occurred yet,

6) The Steering Committee (Pilot Committee) takes decision (see also section 4.4.2: EVALUATION / EVALUATION).

Changes in the national scope. Perspectives beyond 2020.

Over the past three years, the few changes have all aimed to strengthen the notion of belonging to the infrastructure, either by better integration of partners on each of the nodes, or by successive changes **in governance at the national level**. However, on the basis of the founding criteria described above, the FBI has always been involved in **prospecting for new scientific territories**, in the long term. This is one of the reasons why we carried out **the “survey of interest” to join the Infrastructure in 2016**, followed by a multiple-steps audit and consulting process by **our SAB in 2017**. It was made very clear that at the end of the process, the SAB advices will be **presented to the FBI Institutional Committee, for a final decision**. A strategy that arouses debate and reservations within our “Institutional Committee” according to the multiple requirements of the **PIA-INBS Steering Committee**, but that we wish to communicate to the jury in details here, in the perspective of the evolution of the FBI Research Infrastructure and the targeting of new user needs, **in the next 2020-2025 period (See Annex 2 Supplementary Information And Annex 5 -Process For Selection Of New FBI Nodes In The Future-“Declaration Of Interest To Join The Infrastructure”)**

Actual and future changes in the FBI-Nodes internal scopes

While the internal perimeters of the FBI Nodes have **evolved very marginally in previous years**, a number of changes are now on the agenda. **SWOT analyses at the level of Nodes** were constantly performed over this period which took into account the user needs as defined by the requirement of specific services and scientific topics, but also changes in the institutional environment. Based on these analyses each Nodes planed their evolutions in the future. Due to the limited space a synthesis is presented in the **Annex 2. Supplementary Information-ACTUAL AND FUTURE CHANGES IN THE FBI-NODES INTERNAL SCOPES**). This would require an evaluation process inspire from the one applied to **changes in the FBI national scope**.

FBI is a research infrastructure that addresses all the fundamental aspects of life. In this respect, by offering a variety of imaging modalities and corresponding expertise, FBI covers all biological fields.

More precisely, it serves all scientific communities interested in the mechanisms of life and their dysfunctions, at multiple scales of observation. Over the previous period, we have seen the growing interest of materials scientists, particularly in relation to microfluidic and lab on chip approaches. A gain of interest is also to be noted in the fields of ecotoxicology, when these are related to impacts on biodiversity. Finally, in the biomedical field, on the diagnostic side in particular, HCS imaging approaches related to AI developments are within our scope of expertise. An effort with regard to the clinicians and services concerned, as well as in the private sectors of medicines, is under way, which should lead to better adoption of our services and technologies. This will be linked to the redefinition of our outreach and communication plan. In order to define a strategic plan, subcontracting support from *performance consulting companies* is considered.

4.3. IMPACT DU MAINTIEN DE L'INFRASTRUCTURE NATIONALE / IMPACT OF MAINTAINING THE EXISTING NATIONAL INFRASTRUCTURE

4.3.1: SUR LA COMMUNAUTE SCIENTIFIQUE NATIONALE / WITHIN THE NATIONAL SCIENTIFIC COMMUNITY.

As already stated many times in this document, FBI aims at serving all scientists from public and private sectors who are interested in the mechanisms of life. Its specificity is the quantitative analysis of living systems at the multiple scales of observation in normal and abnormal situations, not only in human. Today, FBI serves more than 4500 individual users/year in all fields related to biology, but not only biologists and not only national users. Nevertheless, as estimated in a previous document, we reported to the IBiSA in summer 2018 (**Roadmap for biological imaging**), the number of users on all "IBiSA labelled platforms" at the national level reaches at least 6 500 users (Including FBI core Fs), although with more restricted scopes (local eventually regional) in most of them. As it is, the FBI could not serve much more, especially in the context of Human Resources allocated (120-125 FTEs). The means implemented to take into account the changing needs of this target community are multiple. Regular consultation of our "user committees" both external (**National User Committee**) and respective to Node organizations (**node community**), either by direct interviews or by online surveys that might be general or dedicated to specific topics (*see examples in Annex 3-Surveys and inquiries*) and finally invitation to actively participate to our diverse meetings and workshops. Reciprocally, an extensive participation of FBI scientists and engineers in many scientific meetings not only focused on technologies. We dedicate some **grants-funding** in this respect. The **distributed nature of our RI**, where technological services is matched with particular scientific expertise is an asset in this respect, allowing the FBI to cover all kind of biological topics and more. We also get support and pertinent advices from an international SAB of the highest quality.

Since its inception, the FBI scouted for innovative and emerging technology. This aspect is organic to our overall strategy and constitution (R&D lab associated to core F). It results in invitation of our representatives to an impressive amounts of international conferences and symposium and to the organization and co-organization of the most prestigious congresses and meeting in the field of Biolmaging (ELMI meetings, FOM, two QBIs symposium....) in France. Again, we devote some financial support for this, also for our users, especially for PhD students and post Doc, through "image contest" concourses, for instance. This last example of action is also part of our strategy to promote our RI. In this regard, we are improving our activities towards a wider participation in a

number of trade and business fairs (RDV Carnot; RUE; Salons de L’Innovation, Techinnov, SATT events...). We still have some progress to make in front of us, and are convinced that in this respect we will need to get some help from *performance consulting companies*.

The need to guarantee users reliable terms and conditions for the quality, conservation and even access to the data produced is at the first rank of our next priorities. In this respect we do work with colleagues of other RI at the national landscape (Institut Français de BioInformatique), in the European context with “ELIXIR” (through EuroBioImaging, ELIXIR.FR, EMBRC) and IT departments in particular sites of our Infrastructures (in Institut Curie, ENS and Institut Pasteur). We also launched some “pilots” **with EMBRC.fr and IFB** or in an attempt to do so (with IFB and France Genomique or Profi), in the context of more oriented projects such as HuDeCA (Human Development Cell Atlas), with Inserm.

The project “**My.EMBRC Image**”, which is a joint service operated by EMBRC-France, FBI, and IFB is worth a particular mention. An optimized access to these data is essential for the use of **marine model organisms**, which have become increasingly relevant for many research domains. The “My EMBRC Image” web service enables remote access to a distributed storage infrastructure, cluster computation, and analytical tools, enabling support for the entire image pipeline from acquisition to analysis and through to publication and storage of published images. This pilot project is underpinned by an IFB "sharing of storage and computation resources amongst RIs" support action, and enables the three RIs to deliver a service of interest and relevance to a broad community. The ultimate ambition is to push the service to the international level, involving **EMBRC-, ELIXIR-, and EuroBioImaging-ERICs**.

Other contacts, with **Frisbi nodes** notably, resulted in common local strategies of service implementations (in Cell structural CryoEM or SuperRES- and Fast-CLEM), common support and organization of training workshops and a foreseen common Meeting in summer 2019. A number of scientific consultation and exchanges of expertise in some common technologies have been recurrently performed, notably between the FBI-Paris Centre Node and the Frisbi-Ilkirk Node.

In fact, FBI shares even more with diverse other PIA-RIs in Biology and Health. Indeed, the CBS is part of and involved in the activities of **both Frisbi- and FBI- Montpellier Nodes**. Institut Fresnel in Marseille and UtechS UBI (Imagopole-Pasteur) in Paris Centre **are also funded on projects by FLI**. FBI-BioEmergences in IdF-Sud was a **sub-contractor of Tefor** and FBI-PICT Biophenics is now part of the new RI **CHEMBIOFRANCE**. Finally, while **France Life Imaging (FLI)** systematically refused to engage itself in the participation of the EuBI project, we have hopes that FLI will support us in the future, on our willingness to coordinate training activities within this European framework.

These are only examples of our interaction with other INBS-RIs. At the management level, EMBRC.fr and FBI invited for a first meeting, the representatives of National Coordinations of Celphedia, Frisbi and IFB, all RIs being part of European equivalent, with the aim among others, to draw some common national strategies at the European level. Although premature in its conclusion, this action should lead to greater efficiency in French participation in European RIs in B&H in the future.

4.3.2: SUR LA STRATEGIE DE LA FRANCE A L'INTERNATIONAL / ON FRANCE INTERNATIONAL STRATEGY.

As a previous "Candidate Node" in 2013 for the EuroBioImaging ESFRI project, FBI was qualified at the highest quality (**Highly Recommended**) by the EuroBioImaging International Scientific Committee. FBI is now the only French Node validated as a single entity in the newly **ERIC-EuBI** Research Infrastructure (and France as a founding member since February 2019), one of the **ESFRI "landmark"**. FBI international strategy is reflected in its direct involvement in the internationalization of French biological imaging training initiatives and in its will to be a key actor for training engineering and organization in Europe and beyond.

This strategy can be divided into several levels of action,

1. FBI works for the recognition of French training courses that can be exported internationally. FBI has largely contributed to making the actions of the National Networks in the field known by involving their members into international initiatives.
2. Beside its involvement in other European and International scientific and technological projects, FBI is heavily involved on biological imaging training with other European and international actors (EMBO; Global BioImaging; diverse ITNs in the Marie Curie programs; Twin program RetUBI; FENS-Neurosciences School of Bordeaux, cost Actions such as NeuBIAS, CoMULIS...).
3. FBI is involved in national and international actions to disseminate knowledge and train users, but also core facility staff and managers according to the "Train the Trainers" concept (EuBI WP7 core Facility staff meeting at MiFoBio 2014; GBI-Training in Heidelberg 2016; International Training Symposium at Focus On Microscopy 2017; GBI-Exchange of Experience workshop in Bangalore 2017; GBI-Training in Sidney 2018; Relais RiTRAIN and Corbel).
4. FBI was the coordinator of the working group dedicated to training within the Euro-BioImaging Project (ESFRI Euro-BioImaging Project PPII), and is leading the implementation of the training plan for the future ERIC-Euro-BioImaging infrastructure. Through this role, FBI has two objectives:
 - to develop its own national training plan for biological imaging (see 3.2.5), with the ambition that this plan could be proposed at the European level through Euro-BioImaging.
 - to become the coordinator of the training section of the future ERIC-EuBI infrastructure.

The involvement of FBI, and therefore of the French biological imaging community, at the European level makes it possible to promote the French expertise in biological imaging training and strengthens the role of France as an essential partner for new initiatives/projects for training in Europe and abroad. As such, FBI is involved as partner in **the new project proposal INFRADEV 3 "EuBI ONE"** (Call: H2020-INFRADEV-2018-2020) submitted in March 2019, and will be participating directly in two Work Packages (User access and Node staff training).

Thus, FBI has the ambition to become a European and international resource centre for training, in conjunction with partner institutions (CNRS-Formation entreprises, Réseaux Métiers CNRS, training units of semi-private institutes, Ateliers Inserm, INSTN, etc.) and international organisations (EMBO, EMBL, EMBS, FENS-Cajal, etc.). FBI is also a "reference structure" for emerging National BioImaging communities, such as, the CMI (BioImaging Austria), the Swedish BioImaging community or the Chinese National Biomedical Imaging Center (FBI Director is a Member of the NBIC International SAB; FBI together with PSL Univ and the **Qlife Convergences-Institute** will sign a MoU with **PKU and the**

NBIC, in July 2019 during a “**first Joint Symposium on BioImaging**”), which is scheduled to open in July 2019. The FBI Director is also a member of the Evaluation Board of the CoreFs of EMBL.

4.3.3: DANS LE DOMAINE SOCIO-ECONOMIQUE / IN THE SOCIO-ECONOMIC FIELD.

Pharmaceutical or biotechnology companies (Sanofi, Servier, OGD2-pharma, ABIVAX...) and cosmetics companies (L'Oreal, Clarins...) are "users" of FBI, sometimes in a "service" mode but more often under “contractual terms”. Yet ,we still need to make a strong effort in this respect, since Industrial “Regular Users” from biopharma or biomedical companies are still marginal users of our imaging core facilities (less than 2%). Anatomico-pathologists are other targeted partners, whom we should collaborate in the future. However, with some exceptions (APHP/Institut Curie) our successes are limited. As a first strategy, we engage new development aimed at the integration of the most advanced technologies into HCS/HTP approaches and more automated analysis using deep learning and other AI methods. We plan to install infrastructure "antennas" as close as possible to the services concerned. Some of them are in place (Institut Curie in the translational lab), some others, intended (Bordeaux-Oncosphere). In terms of outreaching, the National Coordination participated to “salons” such as “RDV Carnot” where we met potential “customers” in pharmaceutical companies (BioMérieux, GE...). To open up the field of possible Infrastructure performance, we also entered into negotiations with companies specializing in business performance consulting.

Economic interest: a continuum between research, tech. transfer and companies accessibility to users.

One of the FBI ambitions stated from the initial drafting of our project is to invent and disseminate "bioimaging" technologies and methodologies within our scope and beyond, on partner sites and with companies in the sector. Consistently, another ambition of the FBI is to participate in the reconstruction of an innovative industrial fabric in the field of biological imaging, a sector largely deserted in France, before 2010. One of FBI's successes lies in the evolution of the industrial contracts concluded (operating licences, partnerships and joint laboratories, research contracts and services) over its few years of existence. The FBI, without replacing the valuation structures, encourages the emergence of highly innovative SMEs and VSEs. Some of them arose directly from the RI. FBI supports them internationally through its European and International networks. Most of them are members of the **FBI Industrial Committee**, where they are in contact with major companies in the field (GE Healthcare, ThermoFisher, Leica, Zeiss, Nikon, Minolta...).

In total, all forms of private remuneration (salaries, money, transfers and long-term loans of equipment, free maintenance contracts, royalties, etc.), represented about 0.46 M€ in 2013. **It reached 1.7 M€ in 2017 and 1.2M€ in 2018**, covering about 6% of the total FBI expenses (full cost for 2017; estimated full cost in 2018).

Another aspect which is still difficult to measure at this stage is the indirect effect of the FBI on the socio-economic field. For instance, how many employments the SMEs that we supported in the past or Startups which have their “roots” in the FBI scope will create in the future? What is or will be their turnover? What is the impact of FBI on regional employment areas? How many trained FBI staff will find employment in the private sector (we numbered more than 40 PhD, post Doc, Junior-PIs and Engineers over the FBI period)? Our appreciation is still qualitative at this stage.

4.4. ORGANISATION EN VUE DE LA PERENNISATION DE L'INFRASTRUCTURE / ORGANISATION WITH THE PERSPECTIVE OF SUSTAINABILITY

4.4.1: EVOLUTION ORGANISATIONNELLE DES STRUCTURES DE GOUVERNANCE SOUHAITEE / EXPECTED CHANGES IN THE GOUVERNANCE STRUCTURES.T



New in the organizational Plan for Governance 2020-2025

The Officers. The National Coordination nominates 5 Officers on strategic axes of activities, development and interactions of the infrastructure. These will be preferentially, but not exclusively, chosen among the node coordinators.

Mission Ile de France structuration

The Ile de France Region (Paris Center Node and IdF South Node) representing approximately 50% of the FBI infrastructure activity, with a complex organization and a important evolution of its landscape in recent years, it is necessary for the efficiency of the infrastructure's operation to assign a dedicated officer.

Mission Training and Europe

-Implementation of a single national training passport in interaction with the RCCM, RTmfm networks, the SFμ (French Society of Microscopies), the FBI Core Facility Staff Working Group, the institutional lifelong learning organizations and the Industrial Committee.

-Work with the Manager of the mission Europe to develop the national training passport as a model for the European training passport. The goal and ambition is for FBI to become/be a European/International Training Resource Center and the Training Pilot of EuBI.

Mission R&D

-Responsible for the organization of technology watch in interaction with the Technology Watch Committee and the Technology and Methodology WGs.

-Coordinates, with the National Coordination and Node Managers, the FBI's technological development strategy in interaction with associated R&D laboratories and the potential interested companies of the Industrial Committee.

-Responsible for the FBI survey and technology transfer support of innovations made by associated R&D teams to the platforms of FBI in order to increase the service offer of FBI.

Mission Access/Service

-Responsible for the structuring and visibility of the FBI's service offer, managing the method of access to equipment, and the harmonization of service fees.

-Responsible for monitoring user needs and satisfaction through interactions with the User Committee. Organize, with the **Node Community Officer**, consultation of the representatives of the FBI Node Users Committees (Node Community).

Mission Data Management Plan

-Coordinates with the Image Processing and Data Management Node to identify image analysis needs and contact appropriate R&D teams for methodological developments for the creation of an analysis workflow (to improve the dissemination and impact of the IPDM activities in the overall perimeter of the Infrastructure).

-Coordinates with Nodes and Sites to propose quality and common procedures for the management of image databases and data Centers.

4.4.2: EVALUATION / EVALUATION.

France BioImaging in its current structure already has most of the bodies that will govern the Infrastructure in its sustainability. However, some changes in their operating modes will be necessary (*see Annex 2 Supplementary Information. EVALUATION*). In brief,

-**The committee of partner institutions**, which support the FBI (Institutional Committee) becomes the **Steering Committee of the FBI (Pilot Committee)**.

-**The current FBI-SAB (Scientific Advisory Board or Committee)** is representative of all RI's scientific and service activities, at the highest international level. Its recommendations, systematically transmitted, should be taken into account by the future **Steering Committee**.

-**The User's Committees**. As a distributed infrastructure FBI has both an **external user's committee** (see composition-2018 in Note⁴ in 3.3.1 *Organisation and governance*) and **multiple regional/local user committees** (node community). Their respective roles, modalities and frequency of consultation (online or in meetings) will be stabilized. The appointment and representativeness will be clarified.

-**Projects Committee**. Probably the governance body that will have to evolve the most, notably in the context of **France being part of the European infrastructure "ERIC-EuBI"**.

4.4.3: BESOINS EN TERMES DE RESSOURCES EN PERSONNEL / IDENTIFIED HUMAN RESSOURCES NEEDS

Vital Recruitment Plan to accompany the National Coordination of FBI in its Management

The rational for the following priorities will be explained in the Annex-Supplementary Information

° **Priority 1** Recruitment (IE level) CNRS Operational manager for Europe

° **Priority 2** FBI Administrative and Financial Manager (IR level)

(Note: an FBI Administrative Manager position has been posted on the DIALOG application for the years 2018 and 2019).

° **Priority 3** An Administrative and Financial Assistant position (AI level)

° **Priority 4** A Communication Officer (could be discussed if only for FBI or shared with other RIs; however the important e-communication and Web master activities should be considered)

Recruitment Plan to accompany the development of new service at the FBI Node levels

Finally, thanks to the actions carried out in 2017-2018, we were able to identify the essential resource needs in human technical skills on the five geographical nodes and the IPDM transversal node as part of the infrastructure sustainability. Although we have not yet prioritized these needs among them, a list of **seven to nine "platform" engineers** profiles has been compiled and made available to our main institutions (**CNRS and Ministry of Research-DGRI**). It should be noted that **two of these positions** are in the process of being opened in 2019 (**One in and by Institut Curie** in Paris Centre Node and **one by Inserm** on the Bordeaux Node), more intended in the near future (**Two in Institut Pasteur**, for the **Image Analysis Hub**) and that we intend to solicit our multiple Institutions for these positions, in accordance with their specificities and location. Priority setting procedures are now clarified since 2018-2019. In consultation with the "Institutional Committee" and under the aegis of the InSB-CNRS, the FBI should now be able to establish a "multi-year" prioritization and planning of requests, even beyond 2020-2025. This should pave the road for the reorganization of the RI as a (Very) Large Research Infrastructure (**TGIR**).

4.4.4: MÉCANISMES DE FINANCEMENT DE L'INFRASTRUCTURE / FUNDING MECHANISM OF THE INFRASTRUCTURE.

In 2018, we provided a low estimate, based on the budget and the structure of the expenditure over the period 2014-2016 and the first year over the period 2017-2019. All in all, the FBI Infrastructure runs with a budget comprises **between 65-70 M€ for 3 years**.

- Among the funding assumptions, we considered funding under a "PIA 3 for structuring equipment" (similar equipment and functioning requirements was made for the CNRS –TGIR/IR model in 2019, with projection up to 2029).

- No functioning funding was considered under the envelope that would be available for infrastructure that will have a positive assessment by the end of 2019. **This appears now** in our BUDGET REQUEST (**See Annex 2. Supplementary Information. Budget Request**)

- If the infrastructure has a significant capacity to raise funds for "projects" (optimistically about **1/3 of equipment financing**, should be insured by "exceptional funding") and a high level of services and private contracts (to finance its operating expenses and part of its Human Resources), maintaining its level will only be possible in the context of **infrastructure funding**, from 2020. A slowdown could always emerge in the event that "sustained" funding cannot be obtained. "Sustained" funding is certainly the best lever to rise "extra" ones. While the assumptions considered demonstrate that the

infrastructure can continue to function, it also shows that funding to which the infrastructure could be entitled if positively evaluated will be essential to ensure a ramp-up of biological imaging services and R&D activities in France and to keep its reputation at the international level.

- Finally, the expenditure levels considered reflect an economic balance to estimated revenues. They do not demonstrate the real needs of the various CoreF and associated R&D labs for investment in new or replacement of equipment beyond 2020, which again, clearly depend on the **success of the RI in “calls for projects”**.

Expenditure levels are considered to be achieved at almost constant **Human Resources** on a permanent basis and even decreasing for fixed-term contracts, conditioned here by an expected "strict" evolution of revenues. It goes without saying that without taking the HR needs into account in the future, a stagnation of activity is to be expected and therefore a negative impact on the work and studies of our **users**.

4.4.5: POLITIQUE DE VALORISATION / ECONOMIC VALORISATION POLICY.

One of FBI's successes lies in the evolution of the industrial contracts concluded (operating licences, partnerships and joint laboratories, research contracts and services) over its few years of existence (€1.4M in 2016; €1.7M€ in 2017; €1.3M€ in 2018; about 200-250 % increase since 2013). The market on the medical "biophotonic" side has shown an average increase of 11% over the past 10 years. Unfortunately, France does not have major companies in biological imaging. However, without replacing the multiple structures in charge, FBI encouraged the development of highly innovative SMEs and VSEs. A number of them directly emerged from the RI FBI or flourished with its help. FBI provides expertise and open premises; FBI allow them to benchmark by “testing” innovations; FBI favors contact between these innovative companies with a large variety of Users. Finally, FBI supports them internationally and introduces them to international customers, through its International networks and other scientific contacts (EuBI; ELMI; Global BioImaging; CTLS; FOM...). On pertinent occasions, FBI refers directly to the valorization structures (SATTs, Carnot Institutes, other local or Research National Organization valuation structures,). As a distributed Research Infrastructure depending on multiple Institutions, FBI cannot **have only one contact structure for valuation**, making its policy in this matter quite complicated. Nevertheless, FBI stated ambition is to participate in the reconstruction of a dynamic and innovative industrial sector in biological imaging in France and shows some success records.

4.5. DEMANDE BUDGETAIRE / BUDGET REQUEST

See *Annex 2. Supplementary Information. Budget Request*. Our budget Request, its rational and the economical model we proposed are presented as a table in this Annex 2.

4.6. ENGAGEMENT DES TUTELLES PARTENAIRES / INVOLVEMENT OF PARTNER INSTITUTIONS

See *Annex 6. Letters of Engagement of Partner Institutions*