FRANCE-BIOIMAGING

THE FRENCH NATIONAL RESEARCH INFRASTRUCTURE FOR BIOLOGICAL IMAGING

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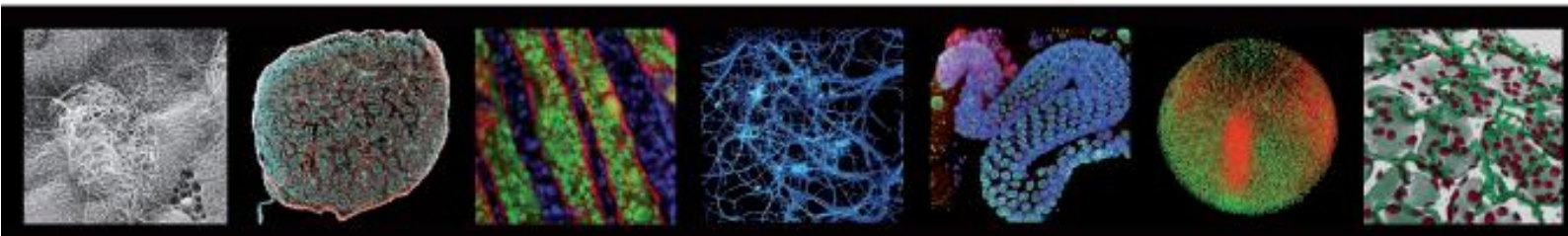
Mid-term Report



Preamble: *France-BioImaging (FBI) was a laureate of the PIA INBS in 2011. The FBI National Distributed Infrastructure has the ambition to* ***develop, promote and provide access to the latest innovations in the field of Imaging for Life Sciences. FBI infrastructure is open to the entire scientific community****, public and private, from France and abroad, for the use of imaging approaches in fundamental and translational biological projects. France-BioImaging is constituted of 5 local Nodes, one transverse Node, and a "light" National Hub for coordination (National Coordination). Each of the local Nodes (Paris-Centre, Ile de France Sud, Bordeaux, Montpellier, Marseille) is constituted by one or several large imaging facilities (most answering the IBiSA requirements) and associated laboratories specialized in the development of new bio-imaging approaches. The transverse Node "BioImage Informatics-Image processing & Data Management" gathers strengths in computational analysis within the overall infrastructure. An expert team from Inria (Inria-Rennes), reinforces this transverse Node.*

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1. Introduction

FBI structure and missions are based on the triptych "Innovation-Access-Training." This association Platforms/ R & D Labs with strong expertise in the various fields of imaging, primary objective of the initial project, served several purposes:

• To Strengthen **the international visibility** of French teams specialized in imaging innovations and promote new collaborations with Life Sciences Scientists.

• To Strengthen the **role of 'infrastructure-platforms"** and their staff in these technological developments and collaborations, by their cutting edge activities at the interface of the aforementioned parties.

• To Promote new approaches and technologies to scientific communities by effective **teaching/training** methods and facilitate infrastructure **accessibility** by integration and/or duplication of FBI innovation.

• To Ensure the efficiency, quality and expertise of "FBI platforms" by strengthening the training of Platform staff, based on a **"train the trainers"** concept.

• To Exploit the potential of a "distributed but coordinated infrastructure" to achieve a common and effective **relationship with the innovative industries** of the area.

A comprehensive understanding of life processes relies on the development of new technologies enabling the multiscale observation and quantification of biological systems. France-BioImaging gathers, in a unique coordinated infrastructure, several outstanding imaging platforms supported by research laboratories in fields related to biological imaging, covering the most recent advances in microscopy, probe engineering, computational analysis and image processing. The overall goal of France-BioImaging is to provide faster access to quantitative measurements and to facilitate an integrative understanding of cellular and physiological activities. FBI welcomes and serves a broad scientific community, from academia to the private sector, beyond the national perimeter.

2012-2014: Preparatory phase: Setting up the distributed National Infrastructure from independent Core Facilities and disseminated R&D Teams

Conceived in late 2011, the FBI investment began at the end of 2012 following a number of necessary administrative requirements. The kick-off meeting of FBI occurred the 27-29th of November and took place at the Institut Curie. The first two years were notably dedicated to setting up and optimizing tools/techniques, an essential phase in order to build the infrastructure as a whole, rather than the simple sum of its preexisting parts. These first two years also served to complete FBI imaging core Facilities with up to date imaging technologies, and to initiate the planned R&D programs. To ensure success at this initial stage, a number of engineers and post-doctoral fellows were hired in 2012-2013, to initiate R&D projects and to set up new services on imaging platforms in the different Nodes. Governance structures were established, their representatives were officially nominated and support staff was hired (one project Manager and later, a part time webmaster). "Networking" activity allowed inclusiveness of external researchers, labs, and other national initiatives to be associated with the overall FBI program. The organization of our "Working Groups" (WG), which parallel the 5 local Nodes + 1 transverse Node, was essential, greatly acknowledged later (March 2014) by our SAB (***see annex 1 FBI-SAB Report)*** and important for the adoption of the FBI project by the French BioImaging community**.** Within these focused WGs, R&D teams directly interact with imaging core Facility staff. It was mandatory for active technological and methodological transfer within and between Nodes. From the beginning, "FBI" was very proactive in the European landscape, in particular within the ESFRI project preparatory phase of Euro-BioImaging (2010-2014). Even in its inaugural phase (2012-2013), FBI was deeply involved in training, taking care "not to re-

invent the wheel". Engaging knowledge dissemination and outreach activities were also pursued (see **5-1 Communication Tools and Strategy. "Inreach" and outreach**)

2014-2016: Gearing up for full operation of the Integrated Infrastructure in Biological Imaging

The full operational phase of FBI as an open national infrastructure began in spring 2014, shortly after the 1st Scientific Advisory Board (SAB) meeting and the subsequent ANR audit. 2014 was a transitional year for the national Coordination. Beside the retirement of our National Coordinator Maité Coppey that was anticipated and announced, we had to face the defection of our Project Manager. We also realized that the coordinated integration of FBI, in particular at a national level, was overly dependent on external factors, such as changes in the strategy or governance of one particular Institute or Research Unit, departure of main FBI members, and insufficient clarity on the budget allocation. We thus adapted both our overall organization, mainly in our internal and external communication tools and modalities and some of our governance structures. Since 2015, all the planned tasks regarding the organizational and logistic aspects of FBI have been delivered. In terms of technology development and services made available, statistics in 2015 show **a rate of achievement comprised between 65-80 %,** depending on Nodes, technologies to be implemented and modifications of the local infrastructures (eg waiting for a new building in IINS-Bordeaux Node, …). During 2014-2015, access modalities and rules, missions, transparency, communication, relative roles and operations at both the Nodal and National levels, have been clarified. A number of dedicated communication activities have been engaged both within and outside of the FBI. Finally, e-communication tools (Web Access portal, bimonthly-newsletter, e-alerts) were created.

2. Governance and Organization: *starting and evolving*

- Governance bodies (*see Annex 2 Governance and Organization. Figure 1) and for details https://francebioimaging.org/about)*

*In **2015-2016,** with the aim to reinforce our consistency, FBI governance scheme was slightly modified:*

- **The National Coordination** is now organized as a **Unité Mixte de Service 3714 CNRS-Institut Curie, "CeMiBio"** (Dir J. Salamero; DR1 CNRS, since January 2015), C. Tessier (CDD; since June 2015) as the Administrative Officer and J. Gallois (CDD; since February 2015) as Webmanager.
- **The Institutional Committee (IC).** Following the "**Consortium Agreement"** finally signed by all FBI-stakeholders in 2015, we established **a new governance body,** the "**Institutional Committee".** It includes representatives of all stakeholders who signed the Consortium Agreement (with ***CNRS** Main Stakeholder)***.** The **IC** takes decisions concerning major changes, composition, and evolution of the FBI infrastructure.
- **The France BioImaging Industry Board.** In 2016, FBI is establishing **the France BioImaging Industry Board (FBIIB).** Representatives of the industrial partners and users were included from the FBI inception. However, the lack of permanent commitment in the ***National User and Advisory Committees*** and the broad diversity of missions allocated to these two Governance Bodies, led to a sub-optimal contribution level by these Partners in FBI development. FBI has now decided to establish the **FBIIB,** which will gather major players in the economic field of Bio-Imaging. We hope to convince them to bring their own view on needed changes to improve the quality of the FBI service offer including training, and propositions to foster technological transfer and partnership. This is an ongoing endeavor still to be proposed and discussed, but the **FBIIB** will also focus on innovative French SME and "start-up" companies. Contacts have been established and responses have been thus far enthusiastic.

- Diversity and complementarity of the FBI infrastructure. Local Nodes share similarities yet also have unique strengths in services and available technologies, or in Research and Development activities (***See annex 2 Nodes specificity and diversity, figure 2**).* This apparent paradox serves two requirements for

BioImaging: Similarities in equipment and "know-how" allow wide access to Regular Advanced Technology at the local/regional level where proximity between biological samples and dedicated instrumentation is mandatory. More sophisticated and innovative imaging technologies and methods, notably those acquired through the first part of the Investment phase of the FBI project (2012-2014), are of course less distributed and to a large extend reflect a diversity in Technology and Methodology expertise as well as in the main biological fields of interest within the Nodes ***(see annex 2 Nodes specificity and diversity, figure 3****).* Finally, nodes differ very much in size and expertise. Each has some kind of personality and specialization. We believe this is strength of FBI.

-FBI "think tanks": our Working Groups. (*see Annex 2 working Groups and figure 4)*. FBI evolution is critically dependent on networking activities that provide new insights into innovative Technologies, new Methodologies and emergent Biological fields of investigation. Aims are to define new avenues, to solve technical barriers and to organize training, thus transferring emerging technologies and methods. They report their results and proposals to the ***NAC*** and ***SAB*** at the "France-BioImaging annual meetings". Some WGs have started to extend their activities in conjunction with other specialized Networks (*WG1a-Super Resolution & Single Molecule Tracking with GDR MIV*) or with other National Infrastructures (for **DATA**, New inter INBS-WGs with ***France Life Imaging and Institut Français de Bioinformatics).*** For details see https://france-bioimaging.org/about/work-packages/

The main objective of the FBI has been to make *"cutting-edge"* and "*emerging"* approaches available to all Users. To succeed, FBI needed to define how to allow this targeted access. It required clear communication between Users and FBI, common procedures accepted by all Node members, precise evaluation of user projects and competencies, to finally guarantee that the right service will be delivered at the right place, in a reasonable timeframe.

-**In 2012**, we participated to the 6 months **Proof of Concept Study launched at the level of the EuroBioImaging ESFRI project** tested our capabilities and experienced some bottlenecks *(FBI executed 30 PCS projects. 27 were trans-national, 22 hosted by our European Champion, the Bordeaux Node)*

-**In 2014**, major technological investments funded by **the ANR-PIA Grant** had been executed and FBI entered its full operation phase. Year 2015 was a critical period in which it had become appropriate to analyze the scientific and R&D impact of FBI. A number of refinements were suggested. In particular, following the recommendation of our ***SAB***, communication "In and out" of FBI, was clearly improved.

-**In 2015,** all elements of our service offering and User access procedures were provided through our open **Web Access Portal** *(see **5. Other Achievements in the France BioImaging Program)***

3. General overview

3-1 Short financial statement. *PIA investment and leveraging effect*

The FBI funding allowed major investments for equipment within Imaging Core Facilities and Associated R&D teams. We invested in turn key high end systems for user access on the Platforms, in particular to re-inforce our service offering in super resolution microscopy, multi-modal Imaging, Correlative Microscopy, *in vivo* and in Depth Imaging and in innovative systems in R&D teams, often concentrating on systems combining several modalities. We also developed high-throughput, high-content pipelines for sample preparation, image acquisition and analysis (*see **4. Scientific and Technological Achievements)*.** As already mentioned, most of the required instruments have been purchased or developed, and the vast majority of them are accessible to the User either directly at the local level or through our **Web Acces Portal**. All in all, **50 to 60 %** of innovative approaches that were planned within the

FBI framework are available to "end users", either directly on platforms or made accessible by R&D associated labs. Consistently, approximately **65% of the deliverables** defined in the FBI program have been attained. Marginal exceptions correspond to ambitious projects (Bordeaux node) or projects that are being revisited due to new emerging concepts (Paris Centre). Thanks to the flexibility of the **ANR-PIA program for INBS, investment will be possible up to the end of 2017**. Another general and direct impact of the FBI investment has been on the level of co-funding**. The original FBI investment (Total Phase 1= 22 M€) already catalyzed a 2.5 fold additional support,** although with discrepancies in the leverage effect between nodes and even between sites within a single Node ***(see annex 2 leverage effects at nodes).*** Worth to note that the FBI program is back-funded by **PIA-Labex programs** *(Deep, CelTIisPhyBio, Inform, SPS, Brain…).*

3-2 Human resources involved in the Nodes and between Nodes. *PIA impact*

FBI funding was also dedicated to Human resources. They are mandatory to the conduct of the overall FBI project in diverse aspects- 1) Supports of transversal activities (Data Management, Communication), 2) Engineers and post-doc fellows recruited from FBI (*33 for about 21 FTPs in 2013; 31 for 15 FTPs in 2015. A total of **750 h.m** since 2012 over **1040 h.m** for the whole investment phase*) or other funding on short term contracts (CDD), to help in systems and new approaches developments, or 3) to steer user projects on sophisticated setups.

In the last period (2014-2016), some newly FBI-recruited and some permanent human resources were affected **to inter-Nodes collaboration and tasks**. It is especially, but not exclusively, true for the BI-IPDM Node for which **2 full time Engineers** are affected to the development and deployment of software platforms (Icy and Mobyle@serpico) and a part-time Research Engineer, with a permanent position at the CNRS, in charge to harmonize Image Data Base development, Data Sharing Strategies and IT solutions, among member sites of FBI.

As innovative technologies and methodologies were progressively introduced, training became a major issue. Our overall strategy is primarily based on a **"Train the Trainers"** approach. FBI is now involved in two large H2020 Projects on this particular aspect (see **5-5 International visibility and activity)** and was recently reinforced, thanks to these latter projects, with **one newly recruited** Support Engineer (hosted by the **Bordeaux Node**).

Another important FBI impact can be measured on human resources sustainability. One FBI funded engineer position in **Bordeaux-Node**, was converted in a CNRS position in 2016 and the **Montpellier node** obtained 2 ITA permanent positions for the FBI project. The **main developer of the ICY platform** got a permanent position at Institut Pasteur in 2015. An Engineer position supported by external funding (LAbex CellTissPhyBio) at the PICT-Curie in **Paris Centre Node**, has been secured at the CNRS, in 2015, while another Engineer is now under a mid-term (COD) contract from Institut Curie for the deployment of a "Small Animal Intravital platform" dedicated to pre-clinical longitudinal studies.

However, a number among us, still fill insecure in their capacity to maintain their required human resources on the long term. It seems critical in particular for **IdF Sud Node. BioEmergences** is still expecting that one of its FBI funded engineers will be stabilized (among 5, 4 having been successively recruited on permanent positions elsewhere). **Imagerie-Gif** recently lost another CNRS engineer (NOEMI CNRS).

3-3 Technological overview

FBI facilitated considerable progress on several flagship projects, via the acquisition of accurate instrumentation, in particular with regards to SUPER-RESOLUTION AND SINGLE MOLECULE TRACKING (24 set up acquired or home-made, on a total of 56), MULTIMODAL & QUANTITATIVE FLUORESCENCE MICROSCOPIES (15 upgrading or acquisitions/39), MULTISCALE AND CORRELATIVE APPROACHES (7/20),

NEW CONTRASTS & IN DEPTH OPTICAL IMAGING (15/32), as well as the application of these technologies to biological questions. Several of these studies have been published in high impact journals by both FBI members and users (***see end of 4.Technological and Scientific Achievements***). FBI teams developed acclaimed innovative microscope architectures. Among them, new instruments, combining multiple imaging modalities with High Resolution Microscopy**,** were notably developed. CLEM/Super-CLEM (**Light/Electronic correlative approaches**) is now among the strongest ongoing developments.

4. Main Technological and Scientific Achievements

In this chapter, selected FBI Scientific and Technological achievements will be presented due to space limitation. We will focus on major technological and methodological innovations and on the Team Building impact of FBI in this respect, **emphasizing Intra-Node and Inter-Node** collaborations.

4-1 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. Thanks to FBI funding, most current High Res. and SMLM modalities are now installed in all Nodes providing Users with state-of-the-art technologies in **super resolution imaging**. This has been accomplished by the purchase of commercial microscopes (PALM/STORM, STED and GSD microscopes) and the transfer of TIRF/PALM/dSTORM setups from R&D associated Labs onto imaging platforms. This also implies new types of services, for designing protocols and 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.

R&D teams, **in the frame of WGs activities**, 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), Adaptive Optics to PALM or SIM to TIRF (IBENS & Neurophotonics, Paris Centre), high axial resolution using Multi-Angle TIRFM and multi-focus microscopy (MFM) combined to Super Resolution by controlling beam diffraction pattern for ultrasensitive multicolor PALM (Institut Curie-Paris Centre). MFM will be soon combined with new technology permitting single plane illumination in single living adherent cells, developed in the Bordeaux-Node (Single objective SPIM). A new instrument based on MFM to acquire SMLM images of thick samples with high time and spatial resolutions was built in Montpellier Node and Collaboration with Institut Curie (Paris Centre) on this method is ongoing. In collaboration with the BI-IPDM node, 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/ and a set of computational tools to reconstruct and visualize 3D data from PALM-MFM is available at http://umr168.curie.fr/en/researchgroups/loco/software/). In the LOB-Ecole Polytechnique, the FBI budget was also 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 approaches are all operating and **accessible to users through the WAP of FBI,** on Imaging Core Facilities, in Bordeaux, Montpellier, Marseille and Paris Centre.

4-2 In Multimodal, New Contrast and In-Depth Imaging

FBI provided key funding for several developments in fluctuation and spectroscopic approaches. **Montpellier Node and some sites at Paris Centre Node,** 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 (e.g. N&B, RICS, PIE-smFRET) methods to directly measure absolute protein numbers in live cells. Funding in **Marseille Node** allowed the purchase of a commercial system (Alba), on which new developments were performed by implementing a STED illumination for FCS measurements in cellular samples. Now, dedicated engineers assist users on this setup for exploratory projects on membrane. However, the major investments in this area were carried out before the creation of FBI. FBI just helped in making them open to the Users, by promoting their integration and transfer onto imaging platforms, notably by training platform engineers. Like in the ***LOB*** (**IdF Sud Node**) our R&D labs are now 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 optomanipulation**. R&D labs developed unique innovation in the type of beam shaping, i.e. *multi-plane spatiotemporally-focused patterns methods* (by combining 3D holographic patterns with temporal focusing) (Neurophotonics Laboratory-Paris Centre). These developments are applied mainly to brain activity measurements through optogenetics tools or to whole-brain functional imaging with two-photon light-sheet microscopy (LOB Ecole Polytechnique, **IdF Sud**). In addition to these unique and innovative techniques, mostly accessible in R&D labs today, other non-linear microscopy systems were developed and set up on imaging core facilities for longitudinal studies in *intravital microscopy* in small animals, in the field of cancer research and on living cells and small organisms (**Paris Centre**).

As one example among many, the development of a combined selective plane imaging microscope (SPIM) and targeted photo-stimulation to activate and image molecular level neuronal mechanisms in brain slices was recently launched **(in Bordeaux)**. It represents a typical common FBI project, as specialized Teams in Bordeaux benefit from external FBI scientific collaborators: Valentina Emiliani (Neurophotonics Laboratory, Paris-Centre node) on wavefront shaping and the team of Pierre-François Lenne (IBDM, Marseille node) for help with the design of the SPIM microscope.

In-house designed light sheet microscopes *(DSLM)* were also set up, transferred to platforms and opened to users in multiple locations (**Paris Centre**, Imagoseine, PICT-Curie; **Marseille**, Picsl). A *novel combination of DSLM and Spinning disk microscope* is currently developed in Paris Centre (on PICT-Curie) through collaboration between IJM and Institut Curie teams. Very recently (March 2016) in **Paris Centre**, Institut Pasteur and Institut Curie, proposed for the first time together, a project at the ***Sesame Program of the Ile De France Region***, named "Multi Scale Light Sheet Microscopy", with the aim to provide all possible modalities using light sheet illumination to the User of FBI platforms. This program is largely based on FBI collaborations beyond the **Paris-Centre node (with Bordeaux; Janelia HHMI, USA; HMS Boston, USA).**

4-3 In multiscale imaging, CLEM & SuperCLEM

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 *(EcCLEM software through ICY, with IPDM-node) and* the development of a new fast automated High Pressure Freezing system coupled to spinning disk confocal microscopy (*1st Prototype of the HFP to be installed* in Institut Curie). 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 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 will be soon installed in

Paris Centre and Marseille Nodes. A major upcoming investment in the **Bordeaux Node** will be the acquisition of a 200 KV cryo TEM microscope that will improve FBI service offer in tomography, and accelerate developments for correlative optical-electronic microscopy in Bordeaux. This investment is waiting for the delivery of a new building in the fall 2016. Other nodes will take advantage of the "know-how" acquired in Paris sites.

4-4 In BioImage Informatics and Data Management; HTP & High Content Screening.

New Image processing suite and analysis tools, developed by the **BI-IPDM Node** partners, are simply impressive. Their dissemination through common and/or open software platforms or web services (Icy, Mobyle@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 creating a new Image Database concept (CiD-iManage/Curie Data Center) or by renting computation access (National infrastructure, France-Grille). Statistics and publications (Web of Science, ***best FBI cited publications***) reflect the ongoing success of the **BI-IPDM** transversal node. 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 (ex: one single image series in DSLM (Digital Scanning Light Sheet Microscopy) produces from 1 to a few Tbytes/day). During the last years, technological advances in automated cell manipulation, 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,** which has significant experience in mRNA imaging in live cells, implemented a high-throughput, high-content pipeline for sample preparation, image acquisition and analysis, a service fully funded by FBI. The main activity of Biophenics (HCS platform part of the PICT platform) **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 a team of the **Computational Biology Center** at Institut Curie, develops new methods for HCS data analysis, combining image analysis, machine learning and data mining. The key purchased instrument at Imagopole (Pasteur) for HCS applications is an automated spinning confocal microscope located in BSL2 environment for the acquisition of live pathogen materials. The data analyses are performed in collaboration with Olivo-Marin team (BI-IPDM node). **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 the project**.

4-5 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 published recently. 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 improved imaging methods and to the emergence of a variety of techniques of photo-manipulation. Different types of probes are in fact associated with different techniques, today developed in France BioImaging: (i) nano-markers are used in electronic and photo-thermal correlative microscopy (**Paris and Bordeaux nodes**), persistent luminescence nanoparticles are used to observing long-term living samples (Paris Centre); (Ii) biosensors for spatiotemporal measures subcellular biochemical activities of proteins such as Rho-GTPases (**IdF-Sud,** Paris Centre); (Iii) the probes and methods for optogenetic techniques (photoactivation/inactivation/cell signaling control) (Paris Centre; **Marseille; Ile de France 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. Finally, they provide information about the function of proteins at high space-time resolutions in single cell, more generally in living tissue.

4-6 Conclusion : Indicators for Scientific Impact of France-BioImaging in terms of Dissemination for Members and Users

In order to evaluate the impact of the FBI project, a list of key performance indicators was established. As a reference date, we took 2013, January 1st. This date was 6 to 8 months after the FBI investments started at the Nodes. Some tasks were already fulfilled at this time and dissemination engaged. However, 2013 is the year when consciousness of belonging to the infrastructure arose among FBI members, the formulation of FBI acknowledgements was clarified and adopted, the first articles on newly developed methodologies and technologies, or using state of the art purchased set-ups, were published. **The list of indicators includes:**

- Number of publications (correctly acknowledged) and impact (h index, for what it means after only 3 years; average Impact factor of publications, by FBI teams and Users) (***See annex 3 Scientific production)[1].*** A short analysis shows the progression from 18 publications in 2013 to more than 80 in 2015 and already 30 as of May 2016. Although three years is an insufficient time interval to measure the true impact of the FBI investment on publication output, it is nevertheless notable to note the **h-index** progression (**3.5** in 2013, **15** in May 2016) of these publications, and an exponential increase in the number of citations (**165** in 2014, more than **600** in 2015 and **260**, 1st May 2016). Perhaps the most interesting bibliometric indicator is the evolution of the average **IF** of FBI papers, from **4.9** in 2013 (18 papers) up to **7.9** for the first 4 months in 2016 (30 papers).

- Qualitative analysis of publications

Statistics reflect 3 major steps in the deployment of the infrastructure:

1) initially, **80-85 %** of articles are published by FBI teams, most papers being based on technology and methodology developments

2) then, Users use new technologies on the imaging platforms or collaborate with R&D teams on newly developed approaches, resulting in **40% of publications by Users mostly co-signed by FBI members** in 2014

3) lastly, newly developed Technologies have been settled or transferred onto one of the FBI imaging platforms; Users are trained and start to publish results using such technologies. In this last period (2015-May 2016) **65% of articles acknowledging FBI (71/110) were authored by Users** (1st and/or last author), with half of them by **Users only**. Interestingly, during the same period, 1/3 of all FBI publications were co-authored by **external Users and Collaborators** (outside the local perimeter of the Nodes), mainly by foreigner colleagues (**25 of 110;** from any place in Europe, USA, China, Australia, Singapore, Japan…).

The evolution of the **Impact factor of Journals** in which FBI articles have been published over the last 3 years, together with the increased number of papers co-authored by Users or authored by Users only, best illustrate the progressive adoption of the advanced technologies and methods developed and acquired by FBI. In turn, it reinforces the impact of FBI on the quality of research by our users.

-Important biological problems explored by Users, the new FBI technologies and methodologies contributed.

To extract specific biological questions from the user projects supported by FBI platforms is both subjective and challenging. In this respect, nodes are regularly asked to indicate 'highlights". In **Montpellier Node**, Marbouty et al. (Mol.Cell, 2015) combined super-resolution microscopy with chromosome

[1] *Numbers were extracted from a "Web of Science" searching, with the key word "France Bioimaging" as funding agency and ANR-10-INBS-04-0x (or **ANR-10-INSB-04-0x, a Recurrent spelling mistake**), as a grant number. Unfortunately, this bibliometric study is far to include all [1]publications from FBI (due to wrong wording, incomplete filling of the Thomson Reuters file by Journals, unpredictability of platform Users…).*

conformation capture methods to dissect the structure and dynamics of a bacterial chromosome. Sanchez et al. (Cell Systems, 2015) benefited from the high-resolution of SMLM to unveil the mechanism of bacterial chromosomal segregation. Tissue morphogenesis/organogenesis is another topic in which recent advance in imaging and in particular light Sheet or MP confocal microscopy, revealed biomechanical mechanisms regulating shape changes or determining progenitor cell positioning, as studied in **Marseille and IdF Nodes**, respectively (Collinet C, et al., Nat Cell Biol. 2015; Munjal A et al., Nature. 2015; Paksa A. et al, Nat Com. 2016). Super resolution approaches and in particular SMLM, have been applied to many aspects in Neurosciences, such as molecular synaptic activity and dynamics (Klaassen RV Nat Com. 2016), while optogenetic approaches revealed that interneurons and oligodendrocyte progenitors form a structured synaptic network in the developing neocortex (Orduz et al., 2015, eLIFE), thanks to the strong expertise in both optical approaches and Neurosciences in **Bordeaux and Paris Centre nodes**. Lastly new FBI technologies installed in FBI nodes have been essential to reveal new fundamental molecular mechanisms in cell biology, at the single cell level, in the field of nuclear organization and transport (Guet D., et al. Nature Com 2015), membrane traffic, cytoskeleton dynamics, cell migration and their interplay (Terawaki S., et al. J. Cell Biol. 2015; Tianyi Y. et al Dev Cell. 2015; Petkovic. J, et al. Nature Cell Biol. 2014) or in cell division (Jord A., et al. Nature. 2014). We should also mention **a clear increase (2 fold)** in invitations of FBI PIs, to prestigious conferences and meetings, both in the BioImaging field (Quantitative Bio-Imaging, ISBI, FOM, ELMI, Neurophotonics…) and in the application fields (EMBO, FENS, Gordon Conferences…) within the last **18 months**. Similarly, an increased number of individual ANRs grants had been declared as impacted by FBI activities (at least 20 Grants between 2012 and 2015, 7 corresponding to **Inter Nodes projects)**. Another interesting indicator (**next section**), is an increased industrial participation to FBI publications, (**more than 10 co-authored papers** in 2015-2016) by both Private Users and Partners.

5. Other Achievements in the France BioImaging Program

5-1 Communication Tools and Strategy *("*Inreach" and outreach*)*

- Intra FBI communication and Team building. FBI was built on a very efficient Networking Activity (***See SAB report in annex 1***). Before the inception of the FBI project, microscopy activities were structured around microscopy facilities and in separated R&D groups from different institutions, at most Nodes. There was little interaction between these structures. The establishment of FBI led to essential synergies at some Nodes. In this respect, since 2014, the National Coordination amplified this evolution, by organizing onsite scientific visits with EB members at all Nodes, dedicated visits of the FBI Administrative Officer, in order to make administrative and support local workforces perceptively active in the project, and thematic visits on transverse interests (i.e. data management survey carried out in 2015). As a representative example, a newly created Scientific Board in Montpellier, in charge of scientific and strategic decisions in the node, is composed by a representative of each of the sited facilities (MRI, iPAM, and the newly created advanced microscopy facility, MARS) and of the R&D groups. Such local reorganization has led to a considerable increase in communication between the different entities **within single Nodes**, in day to day decisions (logistical, organizational, etc), the coordination of new joint activities/projects (teaching, grants..), the discussion of strategic future goals. In the biggest and more distributed FBI-Node, **Paris Centre** (1/3 of FBI Users, 1/3 of FBI R&D teams…), FBI program promoted common meetings on both generic activities of imaging platforms and R&D projects, led to cross access of Users to the different Facilities and to common proposals at different calls (5 ANRs on R&D projects and 2 Sesames IdF in 2016).

- Com and e-com activities

1) The first ***"FBI e-Newsletter"*** was edited by the **National Coordination** in November 2014 and mailed

to 450 contacts. In December 2015, it reached 1227 subscribers. Articles ***link to dedicated pages in https://france-bioimaging.org***

2) Our **Web Site**, its objectives and its content were fundamentally revisited in 2014-2015. The FBI web site is the main FBI centralized tool. Among other services, **"Service offering"** now constitutes the most active part of FBI web site connections (Total: ***10 000 sessions 2015-2016***). All along the year 2015, we built a **"Web Access Portal (WAP)"** aimed to guide Users in benefiting of the Infrastructure. It includes a wide variety of accessible imaging systems for advanced light and electron microscopy, but also screening platforms, data storage facility, software platforms for image analysis (BI-IPDM transverse Node). Finally, training activities organized at both the National and Node ranks, are listed (https://france-bioimaging.org/service-offering). Briefly, The WAP allows **cross-navigation** between Technologies and Methods, Biological fields of Interest and Location. Users provide description of their planned project and other information on a dedicated application form (https://france-bioimaging.org/tools/), addressed to the targeted platform or R&D lab (**FBI sites**) offering the technology as well as to the **National Coordination**. Final decision on where the access is best allowed is taken every month during EB web meetings. Users are then officially informed. Reporting by the user, on the project achievement is mandatory and serves to evaluate and improve service at the FBI site.

3) **Since 2012, FBI was present in many scientific congresses and workshops** at the national and international levels. We organized or co-organized some of them (**16**). Let us mention the organizations of the 13th ELMI meeting in Arcachon (2013), France-BioImaging satellite Symposium at the FEBS-EMBO meeting in Paris (2014), the first Joint QBI-EuBIAS Taggathon (2014/2015, Paris) and the **3 FBI Annual Meetings (**November 2012, March 2014, September 2015) at Institut Curie, Paris. We also supported a large number of other events (**25**). An exhaustive list is accessible on our Website. All demands and propositions (from FBI members, FBI-WGs and others) for support and organization of meetings and training sessions have to be put down on our **"permanently open** call for **Support of Events**". Decisions are taken ***"au fil de l'eau"***. Executive Board members gave seminars for some Institutional boards (CNRS, Aviesan…) and in annual meetings of a number Scientific Societies and Networks (SBCF, SFm, SFB…). FBI activities, missions and objectives were presented to the attendees by FBI representatives.

In the near future, FBI communication activities will still reinforce. An FBI booth will be present at the 16th *European Microscopy Congress* in Lyon and at the *American Society of Cell Biology* in San Francisco. Discussions are ongoing for a strong FBI attendance at *Focus on Microscopy 2017*, Bordeaux.

4) In order to better popularize access to the Technologies and Services offered by the infrastructure, FBI ***launched 2 open Calls end of 2015***

- Call For Scientific Projects for any users from outside the FBI infrastructure. The eligibility criteria are: 1) project requires imaging technology inaccessible at proximity 2) and must be based on an innovative or rarely available technology and/or 3) requires a specific expertise and/or 4) a suitable scientific environment. After validation by the BE and the targeted site, User access is open. FBI co-finances selected projects on travel expenses, accommodation and on experimental costs.

- **Call for Technological and Methodological Transfer Projects.** This call aimed at speeding up dissemination and use of technologies or approaches developed within FBI. Any labs, private or public, or imaging facilities can apply, even from abroad. Acquisition of equipment is not eligible. Financial support is adapted, depending on the nature of the project and its duration, but remains in the order of marginal costs.

These two Calls were surprisingly successful, especially in terms of international impact (*see section 5-2* ***Added value of France-BioImaging in terms of Accessibility).***

1/4 to 1/5 of the **FBI Phase 2** budget (functioning 4 M€; started in 2014) will be dedicated to **Outreach /Com and new Training Activities.** For the latter, **new funded European projects (2015-**

2016) in which FBI is proactive, is helping us to extend our program and plan (***see 5.6 International visibility and activity)***

5-2 Added value in terms of Accessibility: quantitative and qualitative performance indicators

-Impact of FBI on Usage of FBI imaging platform and innovative technologies opened in R&D labs.

The FBI microscopy facilities (IBiSA platforms) already had a large number of local and regional users before the beginning of the FBI project. Consequently, last 2 years, the relative increase due to new users was moderate (from 2589 in 2013 to 3008 in 2015; not including about 1700 new users of software platforms and Image Data Bases proposed by the transverse BI-IPDM Node).

The evolution of running projects (2100 started in 2013, about 2800 in 2015), the nature of used technologies and the origin of Users are probably **better indicators of the FBI impact and access**. Increased project number is primarily due to the acquisition of new "state of the art" technologies on imaging core facilities that help users to better respond to their scientific issues (**see 4.6 Conclusions)**. A closer look shows that, transfer from R&D labs to Platforms also impacted the interest and achievements of Users**.**

The relative numbers of Local (including regional) **versus External Users** (with partition between National and International users) **evolved.** In 2015, the 10 FBI platforms received **180 external demands**, including **40 transnational projects**. Although rather low in proportion, this is positioning **FBI as a major Node** in the future European Infrastructure in BioImaging. In many cases, it led to publications or patents. If one adds collaborative studies (list available on demand) from R&D labs in all Nodes, **external projects** ran on FBI funded approaches, reaches **70 (69** with half as transnational projects)**.** Our "**Open Call for Access",** open in December 2015, already gave rise to **11 selected projects**. Transnational projects, as it was the case during **the Euro-BioImaging Proof of Concept** in 2012**,** are middle to long term (months) projects. They require, travel expenses, hosting capacity, local scientific engagement and continuous human support. Although the FBI infrastructure is not working yet at a full rate (**average of 75% of occupancy** in 2015, in terms of potential hours.year), this indicator does not take into account the human resources available. If the access rate on FBI platforms is moderated by the working time of available expert engineers, rates of occupancy vary from **55 to 100%, leaving little time for further user inclusiveness at a larger scale in some sites.**

5-3 Public-Private relationship & Resulting Socio-Economic impact.

- Measurement of Access level of FBI service by Industrials has always been difficult due to different access modality. With a few exceptions, industrials and platforms do not work on a per hour basis, but rather through contractual projects (sometimes for months or even years), fees are differently calculated (full costs), and requirements for confidentiality or expert support is much more demanding. Nevertheless, the last two years show a clear improvement in our hosting capacity for these Users. L'Oréal, Sanofi Aventis, Galderma are users of Marseille Node microscopes, through **multi-year collaborative contracts**. FBI-Montpellier recorded several ongoing collaborations/interactions with industrial partners over the last 2 years with two screens performed for Metafora Biosystems and Abivax. In Paris-Centre, Institut Pasteur has contracts with Sanofi Aventis and Clarins for histo-pathology analysis of wide-area tissue arrays. Clarins and L'Oreal also work with Institut Curie (PICT-EM) on skin pigmentation, Servier in the development of new biomarkers and OGD2 pharma, for testing and evaluation of new anti-cancer antibodies. 1 to 3% of total occupancy by Industrial Users covers about 10% of the operation incomes on FBI platforms.

- **Collaboration and Technology transfer with industrials.** BioImaging is a very active field in technological development. Consequently, private companies appear rather as collaborators in many technological projects over the FBI infrastructure. A short list of ongoing projects can be consulted in ***annex 3. Scientifc Production.*** Interestingly, French "start-up" companies that were created in the very last years, have their roots in or were supported by France BioImaging (**CryoCapcell, BioAxial and Obsys Scientific;** new instruments in CLEM approaches, High Resolution Microscopy, and Photo-manipulation, respectively). As already mentioned, beside about **40 new patents/licensing** from FBI members (2012-2016; ***list available on demand***), recent co-authorships in international journals is another indicator of the effectiveness of these collaborations. Such an industrial participation to FBI projects was a strong incentive to create the **FBIIB** (ongoing in 2016; see **2 Governance: *starting and evolving)***

5-4 Integration in the "National Infrastructures in Biology and Health (ANR-PIA)" landscape

From the very beginning FBI was in contact with ***France Life Imaging,*** its biomedical counterpart. Both infrastructures share some common scientific interests and overlapping technologies, especially in the preclinical investigations and Image Data processing and mining. FBI and FLI were involved in the preparatory phase of the ***ESFRI project EuroBioImaging***, which proposal is inclusive for both medical and biological imaging. On many occasions, the National coordination met the FLI Copil (Inserm Workshops, Aviesan workshops on biomedical Data). FLI and FBI collaborate through multiple translational projects on cerebral networks involved in normal and pathological behavioral activities or share some optical instrument developed within the FBI framework that are also applicable for in vivo imaging. Similarly, the Structural Biology Infrastructure "***Frisbi"*** is another FBI partner and Electron Microscopy experts from both sides have already organized common workshops and meetings (2 CLEM Days meeting, Paris). ***Frisbi*** and ***Phenomin*** were invited to present their Infrastructures at the FBI annual meetings. These diverse contacts led to joined efforts, such as the definition of secured crossed-access to high-end instruments and methodological expertise or to technology Proof of Concept application studies, combining High Resolution photonic, electron and atomic force microscopy with x-ray crystallography. Finally, common **Working Groups** have been launched recently (2016) between FBI, FLI and **the Institut de Bionformatique Français" (IBF),** in order to define joint programs on **Image Data**. Interestingly, FBI developed unpredicted collaborative activities with other Infrastructures, such as ***EMBRC-France*** *(Banyuls Marine Biology)* or ***TEFOR.***

5-5 Educational and vocational Teaching/Training

As mentioned in our "mantra" **Innovation-Access-Training**, Training is compulsory to allow access to "Innovative imaging approaches", to "end user" on imaging core facility. Our "training" policy takes two aspects into account:

First, FBI is guided by the vigilant care to not "reinvent the wheel". FBI supports, participates or co-organizes teaching and training activities already established by other institutions or research national networks (Inserm workshops, more than 20 CNRS formation-entreprises/year, EMBO courses, practical courses and workshops such as the CNRS thematic School MiFoBio with GDR MIV or in the context of the ZF-Health FP7 EC project …). All FBI Nodes are involved in these national and international training sessions. FBI members participate in educational programs (Master pro, Master 1, 2 and PhD program at Universities (P&M, Diderot and Descartes in Paris; Aix Marseille; Montpellier, Bordeaux, Strasbourg, Tu-Dresden, EMBL Master course…) opens **new programs** on specific emerging tools for biological imaging and contributes to international PhD programs (Advanced Optical Methods for Neuroscience, Univ Paris-Descartes; ITN Symbad, Syndgene; Bordeaux). More particularly, the **Bordeaux Node** is an active partner of the Bordeaux School of Neuroscience that participates to the European neuroscience school program.

In 2014, the IdF node organized the **2nd France-Bioimaging Advanced Training course.** In February 2016, the **Montpellier Node** organized the **3rd France-Bioimaging Advanced Training course** (FBIAT, http://fbiat.weebly.com). The main axis of the course is to provide practical, hands-on experience of very advanced optical setups with a focus on biological questions of interest for the students. The workshop was attended by a large proportion of foreign students (>45%), and ~75% of lecturers from overseas. 95% of attendees (48 students and 20 trainers/lecturers) acknowledged FBI-AT as excellent and will recommend it to their colleagues. A cycle of regular ICY training was set up by **the BI-IPDM node**.

Second, FBI is guided by a "Train the Trainers" philosophy. Because **"**one newly developed technology" means "one new training", FBI aimed at instructing platform engineers on state-of-the-technologies so they can assist users efficiently. This has been instrumental in bringing super-resolution, light sheet techniques or CLEM approaches, to biologists. In this respect, the contribution of FBI R&D labs, was and will be essential. In 2015**, 1800 new users were trained**, while before 2012 the sum of trained scientists in the 10 FBI IBiSA platforms, only reached **1000**. In 2016 we anticipate more than **2000** trainees, **1/3 of them on the newly accessible** setups. In the bottlenecked field of **Image Data**, the transversal BI-IPDM Node proposes new support-service to FBI platform engineers, based on virtual training and tutorials (work in progress). This is mandatory, once taken into account the data deluge produced by new imaging technologies that users have to face. **Vocational training** is thus a challenge and a duty for FBI, in order to stream new knowledge toward its Users. FBI plans to build **new "portfolio and curriculum" at the educational level**, in order to attract new students and to form the next generation of BioImaging Platform Engineers, a relatively new type of career, in expansion on the international scene. Finally, training drives our strategy and activities at the European level in particular through our participation to **2 different H2020 projects** (Global BioImaging and Preparatory Phase II EuroBioImaging) and our strong involvement in the Bioimage Analysis focused **NeuBIAS Cost Action**, in 2016.

5-6 International visibility and activity

- Participation and organization to international activities

As a first indicator for international visibility, FBI strongly impacted the quality of the scientific production and the opening of state-of-the-art-technologies, and as a major consequence, greatly enhanced the attractiveness of Nodes. New teams were recruited in different Nodes, which are advanced users in imaging approaches; FBI had a key impact for the setting of an International Associated Laboratory between IBDM in Marseille and the NCBS in India. In the Bordeaux Node, there was a major success of the call for group leaders launched by the Bordeaux Neurocampus. More than half of 170 applicants had a strong valence in bio-imaging (two 2015 starting ERC awardees working in the field of in vivo multiphoton joined). Similarly, in Paris Centre (last calls for new research team leaders at Institut Curie), 125 out of 150 applicants indicated Imaging expertise as a strong incentive to consider the offered position.

We already underlined the international impact of the FBI program for Users in term of international collaborative studies published in high ranked journals over the past 3 years ***(see 4-6 Conclusion: Indicators for Scientific Impact of France-BioImaging in terms of Dissemination for Members and Users)*** as well as the increase in international demands for access. Each Nodes testifies a real impact of FBI on their attractiveness, such as solicitation for construction of large scale EU and International projects (HSFP, NIH…), building EU consortium and project submissions to FET-OPEN and KET-ICT EU calls. Interestingly, foreign networks have been asking for exchange of experience with ***The transverse BI- IPDM Node*** (Denmark, Austria, Indian BioImaging..).

-A role for France and in particular for FBI, in international training activities

As a candidate node in the EuBI ESFRI project FBI will participate to the EuBI Interim Operation, opening

this summer. As often evoked in this report, FBI has the ambition to play a major role in "training and teaching" activities in bio-imaging. Since this year, FBI is involved in two H2020 projects, EuBI PPII and the H2020 RIA-Global BioImaging, in which France is heading the WP7 Training (Headed by D. Choquet) and a partner for the WG3 Core Facility staff Training (through Institut Curie-Paris Centre Node; with EMBL, Indian, Australian, USA, South Africa, Chili…), respectively. The aim, contents and activities of both projects, cannot be described in details, here. However, let us mention some almost achieved deliverables: organizing surveys on Training Activity and Training Sites for Core Facility Staff and User within the European landscape, and proposing new and necessary "trainings" in the EuroBioImaging frame; organizing virtual and hands-on training Courses, at the world level (1st one planed in November 2016 in Heidelberg). FBI participation and experience, is perceived as a must by our foreign colleagues**.** As a next step, FBI wishes to propose itself as a **"Training Node"** in the frame of the EuBI ESFRI project. Our experience, expertise, equipment of our Local-Nodes with state of the art imaging techniques, in internationally recognized courses activities and virtual training of our BI-IPDM node allow us to propose the largest and most advanced portfolio of "à la carte" trainings in BioImaging over Europe.

6. Perspectives and Prospective

Within the last 1 and ½ year of Phase 1 of the project, some FBI nodes will complete their last equipment acquisitions and development, while this will be marginal in most Nodes. First generation of innovative technologies and methodologies has been already transferred, onto existing or new FBI Core Facilities (e.g. Ultrapole-Pasteur in Paris Centre; MARS in Montpellier). R&D labs and some advanced imaging platforms will continue to open new avenues in revolutionary imaging approaches, for instance in combining high resolution and quantitative measurement of biochemical processes. A strong common activity has been settled in **Paris Centre**. Challenging projects have been planned and started (https://france-bioimaging.org/announcement/retreat-reflections-of-paris-centre-node/), notably with the transverse **IPDM Node** on the development of **BioImage Informatics** tools with the aim 1) to **manage and share Big Data** generated by High Content screening, 3D-Electron microscopy and Full-CLEM, 4D in-depth imaging, or Light Sheet microscopy. 2) to implement **common API interoperability** (as a web service) enabling communication between image analysis software and databases. 3) to propose **e-learning modules** for users. In parallel, the **National Coordination** will reinforce its communication activity, taking care of the global consistency of the infrastructure, and focusing on ***technology and "know-how" transfer*** between FBI-Nodes and with Industry, as engaged the last 2 years.

2017-2019 will be the crucial phase for FBI, in many aspects. Because of space limitation, we cannot detail all envisaged projects and thus only broad and common initiatives will be described. This phase will be guided by the need to give access to innovative **approaches in bioimaging and bioimage analysis**. We will continue and reinforce our networking activity (Working Groups) to facilitate transfer from R&D labs by obtaining support in both funding and human resources. Moreover, following our **"innovation-transfer-training" basic concept,** we will strengthen Training and propose new ways to teach, for both providers (platform staff) and users (mostly biologists).

We posit that the tremendous leverage effect of the PIA-Program will continue to nurture the FBI infrastructure. Our engagement in European and International projects in 2016 is a good sign, although it is difficult to figure out yet whether it will bring in more than just organizational effectiveness, stronger visibility and attractiveness. Fusing both issues on **"funding support and training"**, FBI decided to participate both as one of the **first Hosting Candidate-Nodes** that will operate the Interim phase of the Euro-BioImaging project (summer 2016), and as **The Major Partner** in terms of training and training site definition. In this international context, FBI will lead the training

of the INFRADEV PPII project that will be the main instrument to bring the ERIC EuBI to creation, and will participate to the COST action NeuBias and another EU project, Global BioImaging.

Prospectively, at a longer term, we will foster our capacity to adapt our expertise in the development of technologies with application fields of scientific excellence in the Node local environment. Extension of Node specificity and activity is also envisaged. The prospective schemes which can be drawn today, refer to positioning and opening at the **International level**, improving our industrial partnership, particularly **in the context of Technology Transfer**, developing and promoting **our Training activities,** and building a common **Big Data strategy** for management of the Image resources and analysis, with other National Infrastructures or within the ongoing European structuration (Elixir, BioMedbridges…). In addition to on-going actions, we plan to create a technology transfer platform**,** regrouping engineering expertise and dedicated design/implementation of optical systems for specific scientific projects (Marseille Node). An FBI strategy for both Vocational and User training is engaged at the national and local level. A portfolio of workshops, theoretical and practical courses is proposed, beyond the FBI activity. FBI has the ambition to become a national portal gathering these training activities. A repository of e-training/e-education tools in bioimaging, yet to be developed, could be made accessible through our web portal. In the context of EuBI, France-BioImaging is supporting the opening of a call for **"EuBI Training Nodes**". FBI would be in a very strong position to propose an **integrated Training offer** in bioimaging. The Marseille and Bordeaux Nodes plan to build **Training Centers**. In Paris Centre, an Imaging Training common program is part of the recent official partnership between Institut Pasteur and Institut Curie (February 2016). We do not forget the mandatory **Educational Training/Teaching** in the field of bioimaging. A Joint venture between **Marseille and Montpellier nodes** and inclusiveness between **Paris Centre and IdF Sud nodes** teaching programs should be established**.** At the end**, the "Bordeaux-West Coast, the IdF Training and the French-Mediterranean Training" Nodes**, would make a very complementary proposal of a tripartite **FBI Training/Teaching program.**

One of the best ways to go forward in distributed infrastructures like "France-BioImaging" is to plan its evolution, taking into account new area of technology development, new scientific fields of application, new required needs and changes in the structure itself. In this respect **evaluation** is compulsory, at all levels (national, nodes, site platforms and R&D teams…). As large as its scientific covering could appear, France-BioImaging may still miss some life science communities, applications and even expertise and new methodologies. Its geographic (regional) extension is far from being complete, and other sites, also very advanced in bio-imaging, could certainly be included. For these reasons and for the first time, FBI launched a **"national survey",** with the aim to collect interest from external sites to join the Infrastructure. As main criteria, the proposers had to describe the added value of their project, why it will extend the actual landscape of FBI and to explain their motivation. The survey results were beyond our expectations, with very consistent proposals (from Lille, Illkirch-Strasbourg, Grenoble, Toulouse, Nice, Rennes-Nantes), excellent internal projects and a clear interest in participating to and benefiting of the international visibility and activity of the France BioImaging infrastructure. The next step, in the near future, will be to build the process to integrate new candidate nodes as well as evaluate the existing nodes together with our parent institutions, to shape **FBI V2.0**.

In summary, our strategy for the next years is in four points:

- **Reinforce R&D**
- **Build a National integrated Training Node**
- **Expand the perimeter of FBI for a better integration of the various French sites,** *in order to*
- **Foster our International visibility and attractiveness**