France-Biolmaging Activity Report

2021-2022



Edito

2022 was an important landmark for France-Biolmaging.

In 2022, we celebrated 10 years of operation and scientific advances. This milestone highlights our accomplishments and the long-term goals that France-Biolmaging is committed to reach. By boosting innovation, training scientists and giving users access to high-end technologies, many top notch projects have benefited from the infrastructure and its experts.

Here, we present the last two years of this decade aimed at pushing the limits of biological imaging. This biannual report describes our organization and our mission but more importantly, the events of 2021 and 2022 and the activities launched in these last two years. By giving you key figures, the document acts as an overview of the projects of the infrastructure, its scientists and its users. As our desire is to reach for and to share with the national and international bioimaging world, we also point out a few papers selected for their social impacts and for the transformative role that these studies could play in the future.

Because what is imaging if not seeing beyond?



Edouard Bertrand, Scientific Director of France-BioImaging



> "Little Monster"

©Carole SIRET, Van de Pavert team, CIML Lightsheet Microscopy Winner of the FBI Image Contest 2022



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A national infrastructure

France-Biolmaging is a National Infrastructure in Biology and Health (INBS) laureate in 2011 of the national Program "Investissements d'Avenir" (PIA-ANR) in biological imaging. FBI is at the crossroads between biology, biophysics and engineering, mathematics and informatics. Our unique coordinated infrastructure gathers several large biological imaging facilities and laboratories specializing in R&D for imaging in six local and one transversal Nodes. We aim at creating the most efficient adoption of the latest advances in all microscopy-related technologies and methods by the users of our facilities. These technologies and methods, reinforced by a strong support in computational analysis, provide quantitative measures and integrative understanding of a wide range of cell and tissue activities in biological models, from the simplest, to small animals in normal and pathological situations.

> Missions

FBI is the National Infrastructure in Biology and Health (INBS) in biological imaging. Our primary mission is to develop and provide access to state-of-the-art imaging technologies, innovative approaches and expertise to scientists. With this in mind, we aim at investigating new imaging-related issues in physics, chemistry, applied mathematics & computer science. Finally, our mission is to speed up technology transfer and act as a central hub for collaborative projects.

> Vision

Our philosophy is to associate leading R&D research teams with service facilities. Hence, FBI is at the crossroads between molecular and cell biology, biophysics and engineering, mathematics and informatics. In 2022, our unique infrastructure, structured in 6 local Nodes and one transversal Node dedicated to bioimage informatics, gathers together 20 large biological imaging facilities and 54 R&D teams specialized in imaging. Indeed, in order to develop and provide access to innovative instruments and imaging technologies to scientists, our strategy is to associate leading R&D research teams with service facilities.

> Goals

France-Biolmaging aims at creating the most efficient adoption of the latest advances in all technologies and methods related to microscopy, by the users of the imaging facilities. These technologies and methods, reinforced by a strong support in computational analysis, provide quantitative measures and integrative understanding of a wide range of cell and tissue activities in biological models, from the simplest, to small animals in normal and pathological situations. The tryptic "Innovation, Training, Access" is the backbone of our activities. Thus, we invent and disseminate new imaging technologies, participate in national and international educational and training programs, and make them accessible to national and international users of both the academic and private sectors.

The governance

How does FBI work?



Our Infrastructure is organized in several units: the Executive Board, the Institutional Committee, the Operational Management and the Strategic Management Units.

The **Executive Board** comprises the National Coordination, the Node coordinators and Representatives of the FBI Core Facilities. The National Coordination is formed by a Scientific Director, a Deputy Director for European Affairs, an External Affairs Manager, an Internal Affairs Manager. The National Coordination is supported by Communication and Administrative Services.

The infrastructure is also engaged in several key structuring activities driven by our 7 mission officers and 8 technological working groups (WG).

• Between 2021 and 2022, we organized 21 Executive Board and 2 Institutional Committee meetings.

• In 2021, the Scientific Advisory Board evaluated and endorsed 7 new core facilities and 18 new R&D teams.

• In 2022, we visited the Paris-Centre node.

The **Mission Officers** are working on the development of the infrastructure through different transversal topics: Node structuration, Inter-infrastructure actions, Image data, Training, Facility integration and e-Management, R&D and Tech-transfer and External user needs.

The **Working Groups**, meanwhile, evolve at the crossroads of disciplinary and community development: FBI Technological WG, INFRATECH WG, FBI.data WG, Training Mission WG, etc. They ensure that FBI is aware of the emergent needs of research communities in biological imaging and, in turn, give the infrastructure a platform for engagement with them.

National Coordination & Support Services



Edouard Bertrand Scientific Director



Alexandre Philips Internal Affairs Manager



Alban Belloir Communication Assistant



Daniel Choquet Deputy Director for European Affairs



Caroline Thiriet External Affairs Manager



Zineb Halla Administrative Officer

Key figures of 2022



2350 software platform users



307 scientific staff





113920 h/year of machine use









As we provide access to a multitude of biological imaging technologies and services, we strongly encourage every scientist, both from academia and industry, to contact us.

Here is an overview of the imaging expertise we provide:



> BIOIMAGE INFORMATICS NODE

Bioimage informatics • Data management

Software platforms • AlIA & data visualization • Very large data management & mining







CANCER NEUROSCIENCE RESEARCH

GENETICS &





REGENERATIVE MEDICINE



PATHOGENS

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• • 0

> MARSEILLE NODE

Multimodal Imaging • New contrasts Immunology • Developmental biology

> MONTPELLIER NODE

Functional super-resolution • **High-throughput microscopies** Genome organization • Gene expression

> PARIS-CENTRE NODE

3D CLEM • High content screening • **Optogenetics & biosensors** Host-pathogens • Cancer research







MANAGEMENENT





How to access?

- For local users, access is made through local • reservation tools.
- For external users, as we are the French Node of the European research infrastructure Euro-Biolmaging, France-BioImaging invites them to register through Euro-Biolmaging web portal to access any equipment available on France-Biolmaging facilities: www.eurobioimaging.eu/service. Please contact us if you have questions at contact@france-bioimaging.org.
- For private companies, a single contact to • <u>contact@france-bioimaging.org</u> is at their disposal to answer their requests.

We facilitates the use of our infrastructure and access to high technology by offering academic external users a waiver of facility costs (up to 750€/week).

We are also access provider to the European **ISIDORe project**, which assembles the largest and most diverse research and service-providing instrument to study infectious diseases in Europe, with expertise from structural biology to clinical trials.

Between 2021 and 2022, FBI received, through EuBI 34 requests of access, which makes us a premier user access Node.

Distribution of publications acknowledging FBI by country of co-authors



In 2022,

publications acknowledged France-Biolmaging.

FOR EXTERNAL USERS:

We offer a waiver to external users for the costs of instrument access at FBI facilities.

SUBMIT YOUR PROPOSAL

on Euro-Biolmaging website: www.eurobioimaging.eu

SCIENTIFIC & TECHNICAL VALIDATION



MANY FUNDING OPPORTUNITIES!

France-BioImaging is an access provider for biological imaging in several Horizon Europe projects.

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WELCOME TO OUR FACILITIES!



INNOVATION

Innovation is one of the three pillars of France-Biolmaging. We, facility engineers and R&D scientists, have the common goal and interest at providing state-of-the-art technologies but also developing new ones to have a broader set of microscopy techniques available for our users.

8 Working Groups stimulate scientific 4 FBI structures carry out the technological animation and collaborations: watch: Industrial committee WG1a: Single molecule tracking (15 private sector companies) & Super resolution Technological Watch committee • WG1b: Multiscale light sheet imaging (GdR Imabio, RIME, RTMFM) • WG1c: Multiscale & • Internal user committee correlative microscopies • External user committee • WG1d: Tissue microscopies, new

Moreover, to boost innovation, we created working groups based on networking/ collaborative activities that provide new insights into innovative technologies and emergent biological fields. The objectives are to define new avenues, solve technical barriers and organize training on emerging technologies and methods. These working groups evolve in time to be in line with technological developments and future needs.



Patents registered

since 2011



Collaboration contracts with companies in 2021-2022

2021-2022

contrasts & preclinical applications

 WG2a: High content screening & Intelligent imaging

WG2b: Multiplexed imaging

 WG3: Probe development, **Optomanipulation & Optogenetics**

• WG4: Bioimage informatics, image processing & data management

WG FBI/FRISBI : In vivo structural biology







Boosting technology transfer







In 2021, the first internal call for **«Technology transfer from R&D teams to facilities»** (mature technologies; 5 funded projects) was launched for mature technologies (5 funded projects). In 2022, we then launched outreaching call: **«Novel technologies addressing external user needs»** for immature technologies needing further developments. These actions are part of a long-term strategy for the infrastructure for boosting technology transfer.

«Tech transfer from R&D teams to facilities» 2021 laureates:

- Icy@FBI (Bioimage Informatics Node): Broadening the scope of applications of Icy by implementing several key new bioimage analysis components
- BIC-HCS-SMLM (Bordeaux Node):
 Technological transfer of a Single Molecule-based High Content Screening
 platform to the Bordeaux Imaging Center
- CloudFISH (Montpellier Node): A tool for the analysis of singlemolecule RNA and DNA FISH images
- MorphoNet (Montpellier Node): An interactive online morphological browser to explore complex multi-scale data
- BioImageIT (Bioimage Informatics Node): An open source framework for integration of image data management with analysis

«Novel technologies addressing external user needs» 2022 laureates:

- ModLoc (Ile-de-France Sud Node): Modulated localization microscopy
 - for enhanced in depth imaging of multiple targets
- POLARIMAGING (Marseille Node):
 - Polarized microscopy modalities for molecular organization imaging
- Virtual Microscopy (Montpellier Node):
 - A novel Virtual Reality (VR) approaches to allow a more efficient analysis, navigation, and investigation of volumetric images and videos, produced in fluorescence microscopy.
- LIVECOMICS (Montpellier Node):
 - Combining live cell imaging and in situ omics to understand phenotypic/ transcriptomic relationships in single cells

Innovation and R&D highlights

Bordeaux 2021

New sample preparations & new optics

The Bordeaux Imaging Center offers new services in sample preparation for Expansion microscopy and for Tissue optical clearing & lightsheet microscopy by CUBIC or IDisco techniques. They have also implemented new adaptive optics in Lattice lightsheet microscopy to improve resolution in depth.





Bordeaux 2021

Development of a bioorthogonal labeling of transmembrane proteins with non-canonical amino acids unveils masked epitopes in live neurons

Development of a complete labeling and imaging pipeline using genetic code expansion and non-canonical amino acids in neurons that allows to fluorescently label masked epitopes in target transmembrane proteins in live neurons, both in dissociated culture and organotypic brain slices. This allows us to image the differential localization of two AMPA receptor (AMPAR) auxiliary subunits of the transmembrane AMPAR regulatory protein family in complex with their partner with a variety of methods including widefield, confocal, and dSTORM superresolution microscopy.

Bessa-Neto, D., Beliu, G., Kuhlemann, A. et al. Bioorthogonal labeling of transmembrane proteins with non-canonical amino acids unveils masked epitopes in live neurons. Nat Commun 12, 6715 (2021)

Bordeaux 2022

Technological transfer of the HCS-SMLM technology from Sibarita R&D team to the BIC facility

HCS-SMLM is an automated quantitative single-molecule-based super-resolution methodology that operates in standard multiwell plates and uses analysis based on high-content screening and data-mining software.

> Bretagne-Loire 2021

Development of a new contrast in cellular imaging by using the polarization orthogonality breaking method

This polarization imaging technique, referred to as orthogonality-breaking (OB) imaging, implements micro-wave photonics. Besides, it can be adapted on a classical confocal fluorescence microscope, and can provide informative polarization images from a single scan of the cell sample.

Desapogu R, Le Marchand G, Smith R, Ray P, Gillier E, Dutertre S, Alouini M, Tramier M, Huet S, Fade J. Label-free microscopy of mitotic chromosomes using the polarization orthogonality breaking technique. Biomed Opt Express. (2021) 12:5290-5304.

> Bretagne-Loire 2022

Development of a cell-specific laser ablation protocol

MRic facility developed a cell-specific laser ablation protocol to study development of brown alga S. latissima early embryos under the confocal microscope. Algae belonging to the order Laminariales display embryogenesis patterns similar to Saccharina, this protocol can thus be easily transferred to other species in this taxon.

Boscq S, Dutertre S, Theodorou I, Charrier B. Targeted Laser Ablation in the Embryo of Saccharina latissima. J Vis Exp. 2022 Mar 11;(181).

> Bretagne-Loire 2022

MicroPICell received 2 quality certifications

The MicroPICell facility obtained a dual quality management NFX50-900/ISO 9001 certification for its activities in histology, microscopy and data analysis (service provision, equipment provision, R&D).

> Bretagne-Loire 2022

New equipment for Raman spectroscopy

H2P2 platform acquired new equipment dedicated to stimulated Raman spectroscopy (SRS) in complementarity to spontaneous Raman spectroscopy.

Ile-de-France Sud 2021

A new Method to perform axial localisation at high resolution: the Mod Loc strategy

The use of illumination modulation approach can achieve nanometric axial localization precision by up to several micrometres in depth without compromising the acquisition time, emitter density or lateral localization precision.

Jouchet, P., Cabriel, C., Bourg, N. et al. Nanometric axial localization of single fluorescent molecules with modulated excitation. Nat. Photonics 15, 297–304 (2021).

Ile-de-France Sud 2022 A novel label-free microscopy technique to image red blood cells and oxygenation

Researchers from the Laboratory for Optics and Biosciences of a new form of multiphoton microscopy providing label-free imaging of red blood cells and oxygenation called color thirdorder sum-frequency generation microscopy. This method has the advantage of providing simultaneous measurements at several wavelengths spanning the hemoglobin absorption spectrum.

Ferrer Ortas, J., Mahou, P., Escot, S. et al. Label-free imaging of red blood cells and oxygenation with color third-order sumfrequency generation microscopy. Light Sci Appl 12, 29 (2023).



(a) TSFG color microscopy principles ; (b) Imaging of isolated red blood cells; (c) Imaging of a zebrafish embryo; (d) 3D in vivo imaging in an adult zebrafish brain. © Laboratoire d'optique et biosciences (LOB, CNRS / École Polytechnique / INSERM)

Ile-de-France Sud 2022

Installation of a new SEM and implementation of a new super resolution modality at Imagerie-Gif

- Installation in 2023 of a new scanning electron microscope, equipped with an ion beam (Crossbeam 550, ZEISS), to perform 3D imaging at high-resolution on biological samples.
- Implementation of a new super resolution modality at Imagerie-Gif with the installation of a Lattice-SIM (Elyra 7, Zeiss) to increase the resolution on live and thick samples.

Marseille 2021

Implementation of a NF X 50-900 standard quality approach

The CIML platform has implemented a quality approach according to the NF X 50-900 standard. The main actions carried out were the use of OpenIRIS as a management tool, the implementation of satisfaction surveys after each training session, the planning of metrology measurements and the improvement of communication through the user committee and the management review.

> Marseille 2022

4polar-STORM polarized super-resolution imaging

This new method determines both single-molecule localization and orientation in 2D, infers their 3D orientation, and is compatible with high labeling densities. The method is thus ideally placed for assessing the organization of dense protein assemblies in cells. It is being transferred from Marseille to Institut Curie via FBI outreach 2022.

4polar-STORM polarized super-resolution imaging of actin filament organization in cells. Rimoli CV, Valades-Cruz CA, Curcio V, Mavrakis M, Brasselet S. Nat Commun. 2022 Jan 13;13(1):301.



STORM of zoomed regions of interest (ROI) (squares in (d)). ROI 1, ventral SF; ROI 2, FA; ROI 3, dorsal SF; ROI 4, meshwork. f) δ stick images of zoomed regions (dashed squares in (e)). 4polar-STORM images were repeated independently on three different samples (3-5 cells per sample) with similar results.

> Marseille 2022

PICsL-CIML acquired a spectral confocal microscopy

Installation at PICsL-CIML of a spectral confocal microscopy ZEISS LSM 980 with an infrared detector for the detection of more than ten fluorescent markers at the same time (400-900 nm).

Montpellier 2021

Imaging translation dynamics in live embryos reveals spatial heterogeneities

The Lagha team in collaboration with MRI facility used the SunTag labeling method to image the dynamics of translation of individual messenger RNA (mRNA) molecules in living fruit fly embryos. This work revealed "translation factories"—clusters of mRNA and translation machinery—and heterogeneities in the efficiency of translation between identical mRNAs.

Dufourt J, Bellec M, Trullo A, Dejean M, De Rossi S, Favard C, Lagha M. Imaging translation dynamics in live embryos reveals spatial heterogeneities. Science. 2021 May 21;372(6544):840-844

Montpellier 2022

A pipeline for high-throughput single molecule FISH (HT-smFISH)

smFISH uses single-molecule fluorescence in situ hybridization to visualize RNA in its native subcellular environment. Because of the difficulty to perform systematic experiments in medium- or high-throughput formats, HT-smFISH has been developed as a simple and cost-efficient method for imaging hundreds to thousands of single endogenous RNA molecules in 96-well plates. HT-smFISH uses RNA probes transcribed in vitro from a large pool of unlabeled oligonucleotides. This allows the generation of individual probes for many RNA species, replacing commercial DNA probe sets and reducing the overall costs.

HT-smFISH: a cost-effective and flexible workflow for high-throughput single-molecule RNA imaging. Nature protocols 2023, doi: 10.1038/s41596-022-00750-2



HT-smFISH probe sets hybridized in mouse colon tissue sections and primary neurons. (A) mouse colon tissue extraction and reparation for HTsmFISH labeling. Intestinal crypt cells are depicted in which the mRNA is labeled by probes shown in green. Green dots represent single mRNA molecules. (B) Micrographs of longitudinal and transversal mouse colon sections imaged by widefield microscopy. Left and areen, dots corresponding to single KIF1C mRNA molecules labeled with TYE563; middle and red, autofluorescence of the sample obtained via imaging the mock GFP channel. Scale bars are 10 microns and DAPI stained nuclei are shown in blue.

Montpellier 2022

A Lattice lightsheet at MRI

Installation of the first French Zeiss lattice lightsheet 7 system on the MRI facility, allowing fast and sensitive live imaging.

Paris-Centre 2021

Engineering of a fluorescent chemogenetic reporter with tunable color for advanced live-cell imaging

A collection of fluorogenic chromophores with various electronic properties enables to generate bimolecular fluorescent assemblies that cover the visible spectrum from blue to red using a single protein tag engineered and optimized by directed evolution and rational design. The ability to tune the fluorescence color and properties through simple molecular modulation provides a broad experimental versatility for imaging proteins in live cells, including neurons, and in multicellular organisms, and opens avenues for optimizing Förster resonance energy transfer (FRET) biosensors in live cells. The ability to tune the spectral properties and fluorescence performance enables furthermore to match the specifications and requirements of advanced super-resolution imaging techniques.

Benaissa H, Ounoughi K, Aujard I, Fischer E, Goïame R, Nguyen J, Tebo AG, Li C, Le Saux T, Bertolin G, Tramier M, Danglot L, Pietrancosta N, Morin X, Jullien L, Gautier A. Engineering of a fluorescent chemogenetic reporter with tunable color for advanced live-cell imaging. Nat Commun. 2021 Nov 30;12(1):6989.



Paris-Centre 2022

Development of a 3D custom-access serial holography (3D-CASH) for optical recording of neuronal activity of brain circuits at cellular and millisecond resolution

Built on a fast acousto-optic light modulator, 3D-CASH performs serial sampling at 40 kHz from neurons at freely selectable 3D locations. Motion artifacts are eliminated by targeting each neuron with a size-optimized pattern of excitation light covering the cell body and its anticipated displacement field. 3D-CASH offers access to the millisecond correlation structure of in vivo neuronal activity in 3D microcircuits.

Akemann W, Wolf S, Villette V, Mathieu B, Tangara A, Fodor J, Ventalon C, Léger JF, Dieudonné S, Bourdieu L. Fast optical recording of neuronal activity by three-dimensional custom-access serial holography. Nat Methods. 2022 Jan;19(1):100-110.

b) Confocal micrographs of life and fixed HeLa cells expressing pFAST fused to: histone H2B, lyn11 (inner membrane-targeting motif), LifeAct (actin-binding peptide domain), mito (mitochondrial targeting motif), and to microtubule-associated protein (MAP) 4 and labeled with 5µM HBP-3,5DM. c) Depth color coded three-dimensional reconstruction (from 81 optical sections over 12.8µm) of live HeLa cells expressing lyn11-pFAST fusion and labeled with 5µM HBR-3,5DOM. d) Confocal micrographs of live dissociated hippocampal neurons expressing pFAST fused to lyn11, LifeAct, and MAP4 and labeled with 10µM HBR-3,5DOM.

> Paris-Centre 2022

CyberSco.Py, Python software for advanced automated time lapse experiments

A proof-of-principle of a user-friendly framework that increases the tunability and flexibility when setting up and running fluorescence time lapse microscopy experiments. CyberSco.Py combines real-time image analysis with automation capability, which allows users to create conditional, event-based experiments in which the imaging acquisition parameters and the status of various devices can be changed automatically based on the image analysis.

Chiron L, Le Bec M, Cordier C, Pouzet S, Milunov D, Banderas A, Di Meglio JM, Sorre B, Hersen P. CyberSco.Py an open-source software for event-based, conditional microscopy. Sci Rep. 2022 Jul 8;12(1):11579.



From simple to advanced MDA. (A) Classic Multi-Dimensional Acquisition (MDA) protocol to observe yeast proliferation in a microfluidic chamber, with two imaging channels (brightfield and RFP) imaged every 6 min for several hours. (B) An advanced MDA, in which the user has defined several positions, but set different illumination settings in the blue channel. Each position is exposed to a different level of light stimulation, which alters the expression of a yellow fluorescent reporter both in terms of cell-cell variability, the maximum level of expression and dynamics. Thus, in one experiment, it was possible to quantitatively calibrate the pC120 optogenetic promoter using our settings without any requirement for coding.

> Bioimage Informatics 2021

DeepFinder: a new AI-powered algorithm for the semi-automated analysis of a wide range of molecular targets in cellular tomograms

DeepFinder can efficiently identify molecular complexes with variable shapes and molecular weights within the crowded cellular environment. Importantly, DeepFinder is significantly faster (~10x) than the conventional template matching procedure and performs better at identifying various macromolecules than other competitive deep learning methods. Thus, DeepFinder not only processes large datasets in a single day, but also allows for the simultaneous identification of several macromolecular species. The algorithm's accuracy is comparable to expert-supervised ground truth annotations, but without the need for further complex and time-consuming classification steps. Last, but not least, DeepFinder has been implemented as a free, open-source program with an accessible graphical user interface.

> Bioimage Informatics 2022

Deployment of the BioImageIT software

Software for image management and manipulation, and analysis of optical microscopy images allowing to connect large image databases to image processing pipelines based on heterogeneous components (OS/Linux; Java, python, C++) with metadata storage and processing respecting FAIR principles in data science.

- Collaboration/Deployment/Transfer: 12 microscopy platforms of France-BioImaging
- Number of users: 200-500 users per platform (e.g. Institut Cochin (Paris): operational/functional solution for 350 users and 40 research teams)

S. Prigent, C. A. Valades-Cruz, L. Leconte, L. Maury, J. Salamero and C. Kervrann. BiolmagelT: Open-source framework for integration of image data-management with analysis, Nature Methods, 2022.



BioimageIT: example of data management and processing with a simple python API

TRAINING

STORM : how to get . Dichroic Lens ane :

Beyond its active role as participant and support for training activities in imaging, FBI is also convinced of the importance to build a more integrated training offer to ensure sufficient biological imaging capability in France at all levels and sustainable career pathways.

The future of biological imaging is reliant not just on technologies but more importantly 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.

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85 56 Initial training Institutional training courses courses As part of our structuring activities, we have set up a Training Working Group, whose objective is to provide the infrastructure with life-long training solutions targeted towards its end-users and staff. A large amount of training material exists, but is locally stored, and the tools to make it findable, accessible,

interoperable and reusable are missing. The Training WG has therefore been focusing on the FAIRisation of training material in biological imaging.

This WG gathers representatives of our facilities and national professional networks (RTmfm and RIME) and scientific societies (Sfµ). The transferable knowledge was listed and prioritized in the form of a 3-level mind map: field, topic and sequences.





In 2022

~3100 Users trained in our facilities!





Participation or co-organization of doctoral programs

A **book of knowledge** was thus constituted to facilitate identification of teaching sequences and the navigation within these data and to provide a reading grid for training programs, for each of the 3 fields of activity of the infrastructure: electron microscopy, photonic microscopy and data processing/analysis.

In 2022, the training content developed through these books of knowledge is now used to implement a pilot training program through online modalities with the preparation of **MOOCs**. With this idea of "training the trainers", the working group often organizes workshops for scientists on how to create training material. For example, they learned about how to create video material for the future MOOCs on microscopy and data treatment with theoretical and practical courses and group works.

France-Biolmaging Advanced Training



France-BioImaging, with its partner the GDR IMABIO, organized the 4th edition of the FBI-Advanced Training: an advanced microscopy workshop that was held in Paris in november 2022.





The main objective of the **France-BioImaging-Advanced Training** is to train microscopy users on the most advanced imaging techniques that will allow them to perform molecular studies at the cellular level as well as in thick samples.

The **2022 edition** had plenary lectures given by experts in the microscopy development field. These seminars were advertised as a series and were broadcasted for a large audience. In addition, specific techniques were introduced. Hands-on practicals trained attendants on these techniques every afternoon with state-of-the-art equipment available on several of the Parisian Node Imaging facilities including Institut Curie, Institut Pasteur, Institut Cochin, Institut Jacques Monod, Institut de Psychiatrie et Neurosciences de Paris and ENS Paris.

FBI-AT is a great training event for researchers already trained in basic microscopy willing to become familiar with advanced techniques to answer their specific biological questions, or to be exposed to new developments that will allow them to tackle new questions in their project. 135

514

Number of "**in person**" cumulative attendees at the plenary sessions

Number of "**virtual**" cumulative attendees at the plenary sessions

19

Workshop participants: 7 international & 12 national attendees

STRUCTURING ACTIVITIES



Quantitative analysis of Phallusia embryogenesis

©Guignard et al., 2020 ightsheet Microscopy with automated cell segmentation doi.org/10.1126/science.aar5663

Core facilities integration



Historically, imaging core facilities preceded A working group comprising the 5 Nodes the existence of the national infrastructure. pilot engineers was set up to evaluate As a result, for many years, they developed and disseminate the management tools we operational methods in silo. Now, within have adopted to move the platforms towards the framework of the national infrastructure, an infrastructure-based entity. we need to rethink the overall scheme Over the last few years, we have been working of this organization, both on an operational mainly on 4 areas: scale and in terms of instrument pooling, to give the infrastructure a functional cohesion. Obtaining operating indicators

- through surveys
- Deployment of a common reservation tool
- Adoption of an infrastructure
- platform charter
- Improved mutual knowledge

In 2022, we particularly consolidated the use of **satisfaction surveys and publication tracking** (with the Limesurvey tool), enabling us to collect more than 500 opinions on the infrastructure perimeter, representing a representative sample. This action has been integrated while respecting the framework of existing quality procedures on the platforms. The rebound effect of these surveys is to publicize the existence of the infrastructure among users.

A second success this year was the adoption of a third collaborative working tool (Framindmap), which generates mind maps. We adopted the declarative ontology of instrument families, created by EuroBioImaging. Thanks to these two tools, each node has created a mental map of all the instruments available on all the platforms, creating a dynamic map that can be consulted by anyone on the infrastructure website.

To sum up, **2022 was a pivotal year** between the consolidation of the use of tools previously put in place and the convergence of the platforms' operating modes, which should give us access in 2024 to multi-scale management dashboards from platforms and nodes to infrastructure.









LiveSurvey



OpenIris



FBI.DATA

Biological imaging technologies generates a great amount of data that are very demanding in terms of image processing and data management. The **FBI.data project**, one of the key missions of France-Biolmaging, addresses the questions related to the computational analysis and handling of image data.

New methodological approaches to extract information from massive amounts of image data are definitively required. If not developed concomitantly, the lack of accurate methods in this field can become the real bottleneck of innovative bioimaging approaches. Several lines of research and development can be delineated:

- image processing and analysis solutions for bioimaging data quantification and modeling;
- intelligent image data archival and retrieval;
- high performance computing infrastructures dedicated to massive computational demands.



Quantitative Bioimage Informatics – Image Processing

All technologies offered or developed inside FBI generate BIG DATA, comparable to the volume produced by NGS. Here, we focus on their processing and analysis and perform intensive development of innovative algorithms, software and automation of image treatment workflows.

BioImage Analysis and Data Management

Facing the deluge of Massive Data produced by new technologies requires intelligent image data management, archival and retrieval. Thus, high performance computing infrastructures dedicated to massive computation is mandatory. Knowing the nodes and sites needs in this matter and making a precise survey of strength and weaknesses inside FBI, is its first mission. Then, integration to a common and dedicated infrastructure or association to existing ones in other national INBS or International Networks will be decided.

FAIRisation of Data

The **FAIRisation (Findable, Accessible, Interoperable and Reusable)** of data for Open Science is an initiative fully endorsed by France-Biolmaging. It improves transparency and reproducibility, enhances quality of results, accelerates scientific progress and method development and finally boosts collaboration within the scientific community.

Action 1: Management, Mesocentres & High Performance Computing

- Develop the use of Mesocentres
- Access to High Performance Computing
- Data FAIRisation

> Action 2: Remote image analysis service

Launch of remote image analysis services, based on the existing hub at Institut Pasteur and FBI bioimage analysis network, delivering bioimage analysis services to users for consultative or collaborative projects.

Action 3: Tool Development

- Artificial intelligence: Development of Al approaches and making them available in a user-friendly manner to end-users.
- Visualization of high-dimensional datasets: development of novel approaches for data visualization based on virtual reality/augmented reality.





OUTCOMES

- Recommendation and template for **Data Management Plan**
- New Key Performance Indicators (KPIs) added to annual reports of FBI nodes to measure progress
- Open GitHub: provides image data management codes in open source, and a blog with tutorials & recommendations
- FBI Omero webportal: microscopy image data management decentralised platform helping organise, access and archive data
- Opendesk FBIAS: bimonthly online sessions to advise users on how to unsolve their bioimage analysis questions

> INTERNATIONAL ACTIVITIES

French node of Euro-Biolmaging ERIC





Among our international activities, France-Biolmaging is proud to be the **French node of Euro-Biolmaging**. Euro-Biolmaging ERIC (EuBI) is the European Research Infrastructure for Biological and Biomedical Imaging, awarded the landmark ERIC status by ESFRI and thus recognized as the implemented reference infrastructure in the bioimaging field. Euro-Biolmaging was established as an ERIC at the end of 2019. In 2022, it comprises 17 Member countries and 1 Observer. Euro-Biolmaging is a distributed infrastructure that builds on a set of already existing national and international centers of excellence in imaging technologies: the Euro-Biolmaging Nodes.

These Nodes provide physical or remote access to imaging technologies, deliver training and support the users at all the stages of their research projects with their experienced staff.

France-Biolmaging officially became a founding member of the Euro-Bioimaging research infrastructure in March 2019. We have been an active collaborator in the development of the future infrastructure since its inception in 2009 as well as during the preparatory phases of the Euro-Biolmaging ESFRI project (2010 – 2018), and has been a "Node Candidate" of the project between 2013 and 2019.

France-Biolmaging was officially ratified as Euro-Biolmaging French Node in 2019, opening the premises of France-Biolmaging core facilities to external users for access and training activities.

Horizon Europe projects

The campaign led in 2021 by the EuBI ERIC was successful, resulting in **9 Horizon Europe Projects** awarded in 2022, with FBI participating as access provider in 3 of them. These projects aim to facilitate trans-national access to infrastructures' services to the broad scientific community. Each project is targeting a specific field: infectious diseases and COVID for the ISIDORe project, Cancer research for the CANServ project and Agronomy and Ecology for the AGROServ project.

FBI is also a partner in the INFRATECH project ANERIS dedicated to the design of new instruments and methods for sensing marine-life. FBI will lead the development of a technology to process the data from the different imaging and biooptic systems in ANERIS and participate in the dissemination of developments and training to the other nodes.



Access to Euro-BioImaging French node services takes place through the Euro-BioImaging web portal at www.eurobioimaging.eu.

This portal should be used by all national and international users from outside FBI's perimeter.

Partner of Global Biolmaging network

Global BioImaging (GBI) is an international network of imaging infrastructures and communities, which was initiated in 2015 by a European funded project. Recognizing that scientific, technical and data challenges are universal rather than restricted by geographical boundaries, it brings together imaging facility operators and technical staff, scientists, managers and science policy officers from around the globe, to network, exchange experiences and build capacity internationally.

It provides a unique opportunity for international discussion and cooperation to tackle the practical challenges as well as the strategic questions linked to operating open access infrastructures for cutting edge imaging technologies in life sciences.

In 2022, GBI gathered ten National Communities on top of the European Consortium represented by the ERIC-EuBI. In the previous phase (2015-2018), France-BioImaging actively participated in the Work Package 3 "Training Courses for Facility staff", which aimed at publishing international recommendations for imaging facility staff training. Since 2019, France-BioImaging is involved in the Working Group on training, whose aim is to build and structure GBI training resources and in GBI social impact of imaging infrastructure working group, whose work led to the publication in 2020 of a white paper on International recommendation for measuring imaging core facility impact: Key Performance and Social Economic Indicators.





FBI also actively participates in Global BioImaging annual international workshops called **Exchange of Experience (EoE)**, which represent key moments for the international imaging community to come together and discuss common goals, trends and challenges in running open access imaging facilities across the globe. The Global BioImaging 7th edition of the Exchange of Experience was organized with Latin America BioImaging in Montevideo, Uruguay, in September 2022. We presented FBI initiatives for open access, training and discussed collaborative projects opportunities with the Latin-american community.

These workshops are also a fertile ground for France-BioImaging outreaching activities as they allow us to understand emerging bioimaging communities' needs, provide ways to work together with the common goal of scientific advancement and innovation, bring new perspectives and spur on novel developments.

With this in mind, we engaged in a new outreach activity toward the African Imaging Community, in partnership with the African BioImaging Consortium and Imaging Africa, to strengthen the collaboration between African and French researchers in biology. Two dedicated calls for projects to open FBI core facilities to researchers in Africa that have interest in using advanced microscopy approaches for their own research programs and projects are planned for 2023.

SOCIAL IMPACT

How the imaging technologies and image analysis tools available on FBI nodes can answer timely research questions? Here are a few stories contributing to the development of our global society.

> ©Frédéric FERCOQ, PPL, MNHN Confocal Microscor 3rd place of the FBI Image Contest 2022

PLANT BIOLOGY Bordeaux

The lipid composition of organelles acts as a landmark to define membrane identity and specify subcellular function. Phosphoinositides are anionic lipids acting in protein sorting and trafficking at the trans-Golgi network (TGN). In animal cells, sphingolipids control the turnover of phosphoinositides through lipid exchange mechanisms at endoplasmic reticulum/TGN contact sites. In this study, they discovered a mechanism for how sphingolipids mediate phosphoinositide homeostasis at the TGN in plant cells. Together, the data identify a mode of action of sphingolipids in lipid interplay at the TGN during protein sorting.

SARS-COV-2 INFECTION INDUCES THE **DEDIFFERENTIATION OF MULTICILIATED CELLS** AND IMPAIRS MUCOCILIARY CLEARANCE



Robinot, R., et al. (2021). SARS-CoV-2 infection induces the dedifferentiation of multiciliated cells and impairs mucociliary clearance. Nature Communications, 12(1), 4354. doi:10.1038/s41467-021-24521-x

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SPHINGOLIPIDS MEDIATE POLAR SORTING **OF PIN2 THROUGH PHOSPHOINOSITIDE** CONSUMPTION AT THE TRANS-GOLGI NETWORK



Ito, Y., Esnav, N., Platre, M.P. et al. Sphinaolipids mediate polar sorting of PIN2 through phosphoinositide consumption at the trans-Golgi network. Nat Commun 12, 4267 (2021). doi. org/10.1038/s41467-021-24548-0



Understanding how SARS-CoV-2 spreads within the respiratory tract is important to define the parameters controlling the severity of COVID-19. Scientists have shown that SARS-CoV-2 replication causes a transient decrease in epithelial barrier function and disruption of tight junctions, though viral particle crossing remains limited. Rather, SARS-CoV-2 replication leads to a rapid loss of the ciliary layer, characterized at the ultrastructural level by axoneme loss and misorientation of remaining basal bodies. Motile cilia function is compromised by the infection, as measured in a mucociliary clearance assay. Thus, this study identifies cilia damage as a pathogenic mechanism that could facilitate SARS-CoV-2 spread to the deeper lung parenchyma.

CANCEROLOGY Bretagne-Loire

Raman spectroscopy is an imaging technique that has been applied to assess molecular compositions of living cells to characterize cell types and states. Here, scientists provide firm evidence that cellular Raman spectra (RS) and transcriptomic profiles of glioblastoma can be computationally connected and thus interpreted. They were able to predict global gene expression profiles by applying the calculated transformation matrix to Raman spectra and vice versa. From these analyses, they have extracted a minimal gene expression signature associated with specific RS profiles and predictive of disease outcome.

INTEGRATION OF RAMAN SPECTRA WITH TRANSCRIPTOME DATA IN GLIOBLASTOMA

Raman Group 1 - Raman Group 2

Le Reste, P.-J. et al.(2021). Integration of Raman spectra with transcriptome data in glioblastoma multiforme defines tumour subtypes and predicts patient outcome. J Cell Mol Med. 2021 Dec;25(23):10846-10856. doi: 10.1111/jcmm.16902.

GENETIC CODE EXPANSION TO VISUALIZE HARD TO LABEL PROTEINS



Bessa-Neto D et al, (2021) Bioorthogonal labeling of transmembrane proteins with non-canonical amino acids unveils masked epitopes in live neurons. doi:10.1038/s41467-021-27025-w.

NEUROSCIENCE Bordeaux

The explosion in the development of highresolution and super-resolution imaging calls for new approaches to label targets with small probes. This study reports the development of a complete labeling and imaging pipeline using genetic code expansion and non-canonical amino acids in neurons that allows to fluorescently label masked epitopes in target transmembrane proteins in live neurons. With this technique, scientists are able to image the differential localization of two AMPA receptor (AMPAR) auxiliary subunits of the transmembrane AMPAR regulatory protein family in complex with their partner with a variety of methods including widefield, confocal, and dSTORM superresolution microscopy.

DNA Paris-C

DNA DAMAGE Paris-Centre

Heterochromatin is a critical chromatin compartment, whose integrity governs genome stability and cell fate transitions. Here, scientists established a system for targeting UV damage to pericentric heterochromatin in mammalian cells and for tracking the heterochromatin response to UV in real time. Using a laser scanning confocal microscope equipped with a 266 nm laser for UV-C DNA damage, they unveiled a central role for the methyltransferase SETDB1 in the maintenance of heterochromatic histone marks after UV. SETDB1 coordinates histone methylation with new histone deposition in damaged heterochromatin, thus protecting cells from genome instability and UV-involved DNA damage.

ORP5/8 AND MIB/MICOS LINK ER-MITOCHONDRIA AND INTRA-MITOCHONDRIAL CONTACTS FOR NON-VESICULAR TRANSPORT OF PHOSPHATIDYLSERINE



Monteiro-Cardoso VF, et al. ORP5/8 and MIB/MICOS link ER-mitochondria and intramitochondrial contacts for non-vesicular transport of phosphatidylserine. Cell Rep. 2022 Sep 20;40(12):111364. doi: 10.1016/j. celrep.2022.111364. Mitochondria are dynamic organelles essential for cell survival whose structural and functional integrity rely on selective and regulated transport of lipids from/to the endoplasmic reticulum (ER) and across the mitochondrial intermembrane space. As they are not connected by vesicular transport, the exchange of lipids between ER and mitochondria occurs at membrane contact sites. Here, this study reveals a physical and functional link between ER-mitochondria contacts involved in lipid transfer and intramitochondrial membrane contacts maintained by the mitochondrial intermembrane space bridging (MIB) / mitochondrial contact sites and cristae junction organizing system (MICOS) complexes.

IMAGING THE RESPONSE TO DNA DAMAGE IN HETEROCHROMATIN DOMAINS



Fortuny A, Chansard A, Caron P, Chevallier O, Leroy O, Renaud O, Polo SE. Imaging the response to DNA damage in heterochromatin domains reveals core principles of heterochromatin maintenance. Nat Commun. 2021 Apr 23;12(1):2428. doi: 10.1038/s41467-021-22575-5

CELL BIOLOGY Ile-de-France Sud



IMMUNOLOGY Marseille

Lung-resident memory B cells (MBCs) provide localized protection against reinfection in respiratory airways. Here, scientists found that two main distinct subsets of MBCs colonized the lung peribronchial niche after infection. These subsets arose from different progenitors and were both class switched, somatically mutated, and intrinsically biased in their differentiation fate toward plasma cells. Combined analysis of antigen specificity and B cell receptor repertoire have shown that the diverse transcriptional programs in MBCs are not linked to specific effector fates but rather to divergent strategies of the immune system to simultaneously provide rapid protection from reinfection while diversifying the initial B cell repertoire.

VIRAL INFECTION ENGENDERS BONA FIDE AND BYSTANDER SUBSETS OF LUNG-RESIDENT MEMORY B CELLS THROUGH A PERMISSIVE MECHANISM



Gregoire C, et al. Viral infection engenders bona fide and bystander subsets of lung-resident memory B cells through a permissive mechanism. Immunity. 2022 Jul 12;55(7):1216-1233.e9. doi: 10.1016/j. immuni.2022.06.002.

SHORT O-GLCNACASE IS TARGETED TO THE MITOCHONDRIA AND REGULATES MITOCHONDRIAL REACTIVE OXYGEN SPECIES LEVEL



Pagesy, P. et al, Short O-GlcNAcase Is Targeted to the Mitochondria and Regulates Mitochondrial Reactive Oxygen Species Level. Cells 2022, 11, 1827. https:// doi.org/10.3390/cells11111827



In this study, scientists have shown that S-OGA is preferentially targeted to the mitochondria, where it appears to modulate Reactive Oxygen Species (ROS) levels. Mitochondria is believed to be the main source of cellular ROS. Whereas H₂O₂ can act as a signaling molecule in the cell, excess ROS production and elevated H₂O₂ levels have deleterious effects and are involved in several pathological conditions, including cancer, inflammatory diseases, Type 2 diabetes, neurodegenerative diseases, and aging. Therefore, the use of mitochondria-targeted small molecules has been proposed as a potential therapeutic strategy, most notably to specifically deliver antioxidants to this compartment.

CANCEROLOGY Ile-de-France Sud

Fibroblasts actively contribute to tumor progression. In particular, by altering the extracellular matrix and secreting soluble factors, they modulate cancer cell migration. Scientists observed that fibroblasts deposit a network of tubular fibers (tracks) on their migration path. By interference reflection microscopy, they have observed that these tracks stem from adhesion sites of the fibroblasts and remain stably anchored to the substrate. Moreover, they have found that cancer cells would recognize tracks and specifically adhere to them by using clathrincoated structures to grab them. In this study, they propose that fibroblast tracks represent a topography-based intercellular communication system capable of steering cancer cells migration.

IMAGING TRANSLATION DYNAMICS IN LIVE EMBRYOS REVEALS SPATIAL HETEROGENEITIES



Dufourt J, Bellec M, Trullo A, Dejean M, De Rossi S, Favard C, Lagha M. Imaging translation dynamics in live embryos reveals spatial heterogeneities. Science. 2021 May 21;372(6544):840-844. doi: 10.1126/ science.abc3483.

FIBROBLASTS GENERATE TOPOGRAPHICAL CUES THAT STEER CANCER CELL MIGRATION



Baschieri, F et al., Fibroblasts generate topographical cues that steer cancer cell migration, bioRxiv 2022.09.06.506801; doi: https://doi. org/10.1101/2022.09.06.506801



During development, precise control of gene expression establishes reproducible patterns, leading to the formation of organs at the right time and place. The emergence of developmental patterns has been primarily studied at the transcriptional level, but the fate of these transcripts has received little attention. Here, scientists used the SunTag labeling method to image the dynamics of translation of individual messenger RNA (mRNA) molecules in living fruit fly embryos. This work showed that "translation factories"-clusters of mRNA and translation machinery-and heterogeneities in the efficiency of translation between identical mRNAs.

COMMUNICATION & OUTREACHING

The communication link with others"

©Magalie BENARD, PRIMACEN Confocal Microscopy 2nd place of the FBI Image Contest 2022 Those two years have been essential for the development of the communication strategy of France-BioImaging. Following its communication plan, we led multiple actions and diversified our tools to better connect with the national and international bio-imaging community. Therefore, France-BioImaging recently recruited a communication assistant to strengthen the visibility of the infrastructure and expand its outreach.

Website

Multiple types of content are posted on France-Biolmaging's website.

On one hand, the first goal is to promote the community building activities coming from both the infrastructure and our nodes (core facilities and R&D teams). Thus, news about events, job offers, workshops, calls etc. are frequently published.

On the other hand, we have started a new kind of content highlighting the work of our scientists by posting popularized articles of scientific publications. Beside putting forward science, this content aims at reaching a different population.

France-Biolmaging We develop, disseminate and give access to cutting-edge t

in biological imaging.
FRANCE-BIOIMAGING IS A NATIONAL INFRASTRUCTURE IN BIOLOGY AND HEALTH.
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Twitter



Started in 2020, Twitter has now become our main social media. With 1100 followers at the end of 2022, our community is growing step by step. In general, Twitter strengthened the bond between our infrastructure and the broad bioimaging national and international community.

Our tweets mainly consisted in promoting our infrastructure or core facilities, in highlighting calls and fund but also events organized or coorganized by France-BioImaging. Our Twitter strategy is primarily focusing on promoting our website content. With its own editorial policy, we publish about our news but also highlight scientific publications where our bioimaging experts are the coauthor or publications of our users. Besides, Twitter is a good way to highlight events in real time by providing insights. Therefore, we "live tweet" during our community building events with photos of conferences or workshops.

Moreover, we aim at developing our Twitter community by interacting with structures linked with us (e.g. Euro-BioImaging, our core facilities, other european nodes...). Finally, we renewed our Image Contest in order to create more interaction with our community and to display the work of our core facilities' engineers.



Linkedin



France-BioImaging

Services de recherche · Montpellier · 643 abonnés

France-BioImaging decided to launch a Linkedin Because of how this social network works, account to broaden its outreach. Linkedin has Linkedin adds another dimension to our been an important addition to our strategy communication strategy. Since late 2022, as we use this social network to highlight our we developed more engaging content events and job offers. Besides, Linkedin was a about microscopy technologies and their useful mean of communication regarding FBI advantages to further promote the expertise calls. Our main objective in 2021 was to start to of France-BioImaging. build a community around France-BioImaging and to engage connections with biology and imaging professionals.



We develop, disseminate and give access to cutting-edge technologies and methods in biological imaging





FBI Annual Meeting

In 2022, we were finally able to organize our **France-BioImaging Annual Meeting** in person!

After two years of absence, we were glad to be together at the **Bretagne-Loire node in Nantes** with the national coordination and scientists from all our nodes. 2022 was an important landmark for France-BioImaging and its community, as the infrastructure was celebrating 10 years of operation and scientific advances.

The event was the occasion to celebrate this milestone with all the members of the bioimaging community (within and outside the France-BioImaging community). The Annual meeting highlighted France-BioImaging's development as a research infrastructure and its node community accomplishments during these last 10 years, and the role they play in boosting innovation in bioimaging. Imaging scientists and users from the infrastructure's nodes presented their key projects and demonstrated how they have benefited from France-BioImaging and its community!



FINANCIAL DATA

France-BioImaging is funded by the Programme d'Investissements d'Avenir (PIA) since 2012 (grant Agence Nationale de la Recherche, number ANR-10-INBS-04, 26M€). Successfully evaluated in 2019 by the ANR, the additional funding (3,2M€) allows the development of new projects for the 2020-2024 period.

The main funding actions planed are:

- Support for external user access to FBI core facilities: 290 k€
- Working groups, meetings, technology workshops: 850 k€
- Training activities: 275 k€
- Data management & image analysis: 430 k€
- Technology transfer: 770 k€





Partner institutions

CNRS Aix-Marseille Université Collège de France Ecole Normale Supérieure Ecole Polytechnique Généthon Inria Institut Curie Institut Gustave Roussy Institut d'Optique Graduate School Institut Pasteur Inserm Université de Bordeaux Université de Montpellier Université de Nantes Université de Paris Université Paris-Saclay Université de Rennes 1 Sorbonne Université

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