

## EVALUATION REPORT OF THE UNIT

INEM - Experimental and Molecular Immunology  
and Neurogenetics

### UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université d'Orléans

Centre national de la recherche scientifique -  
CNRS

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**EVALUATION CAMPAIGN 2022-2023**  
GROUP C

Report published on June, 26 2023



In the name of the expert committee<sup>1</sup>:

Peter van Endert, Chairman of the committee

For the Hcéres<sup>2</sup>:

Thierry Coulhon, President

Under the decree n° 2021-1536 of 29th November 2021:

<sup>1</sup> The evaluation reports "are signed by the chairperson of the expert committee". (Article 11, paragraph 2);

<sup>2</sup> The president of the Hcéres "countersigns the evaluation reports established by the expert committee and signed by their chairperson." (Article 8, paragraph 5).

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

## MEMBERS OF THE EXPERT COMMITTEE

**Chairperson:** Mr Peter van Endert, Université Paris Descartes

**Experts:** Ms Anne-Sophie Armand, Université Paris Descartes (representative of CNU)  
Mr François Leulier, CNRS, Lyon  
Ms Sophie Novault, Institut Pasteur, Paris (supporting personnel)  
Mr Abdelhadi Saoudi, CNRS, Toulouse (representative of CoNRS)

## HCÉRES REPRESENTATIVE

Ms Anne-Marie Di Guilmi

## CHARACTERISATION OF THE UNIT

- Name: Experimental and Molecular Immunology and Neurogenetics
- Acronym: INEM
- Label and number: UMR7355
- Number of teams: 2
- Composition of the executive team: Ms Valérie Quesniaux

## SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE4 Immunité, infection et immunothérapie

## THEMES OF THE UNIT

Work in the research unit INEM (Immunologie et Neurogénétique Expérimentales et Moléculaires) deals with immunology and neurogenetics. The unit is composed of two teams, each focusing on one of these keywords. Team 1 is interested mainly in lung immunity; it studies lung pathologies related to infection and inflammation for one subgroup, and allergy for the other subgroup. The second team also has two subgroups that are interested in developmental neurotoxicity, neurogenetics of autism and mental deficiencies, respectively.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The unit INEM located in the Orléans CNRS campus was originally created in 2001 and underwent some restructuring events: in 2009, a team working on development left and, in the same period, a team specialized in neurogenetics arrived. A unit with the present designation and present director was then formally created in 2012. The subdivision of each team in two subgroups was initiated in 2015, with the creation of the subgroup focusing on lung inflammation in team 1, and of the subgroup studying developmental neurotoxicity in team 2. Finally, the immunology subgroup led by the unit director repositioned its research to allergy with the arrival of a senior scientist with the corresponding expertise in 2020.

## RESEARCH ENVIRONMENT OF THE UNIT

The INEM scientists have the ambition to link their fundamental and mechanistic research with translational and transversal approaches through contacts with private companies and hospitals, taking advantage of the companies involved in drug production in the Centre Val de Loire region. INEM has a long-standing tradition in collaboration with pharmaceutical companies, patent registration and start-up creation.

International collaborations of INEM include a contribution to an Inserm-Helmholtz (Allemagne) program committed in lung inflammation, a participation in two CNRS International Research Programs: one with South Africa focusing on TB immunity which gave rise to an extension through the "Protea" project, and one involving the university of Sao Paulo in Brazil ("Immune response to danger signals").

At the regional level, INEM has been a founding member of two thematic research networks focusing on Infectiology (FED 4225) and on Functional Neuroimaging (FED4226). At the local level, it contributes to a thematic research network "Motivhealth", to the "GDR" Plasma Medicine, and it benefits from two local "*Investissement d'Avenir*" programs (Minerve, Loire Val Tech).

INEM has been involved in creating the spin-off ArtImmune in 2010 and the joint laboratory ArtINEM in 2016. It takes part in the steering committee of a regional "Biopharmaceutical Research Program" and has obtained the Maturation Project "Pulmo Protect". It is a member of the regional "Technology Transfer Booster Program".

Finally, members of the Neurogenetics team have responsibilities in the regional Orléans hospital and obtained one orphan drug designation linked to creation of the startup KAERUS in 2016. Physicians in the unit also take part in a regional hospital consortium (Fédération GenoMedS).

## UNIT WORKFORCE: in physical persons at 31/12/2021

<b>Permanent personnel in active employment</b>	
Professors and associate professors	3
Lecturer and associate lecturer	6
Senior scientist (Directeur de recherche, DR) and associate	2
Scientist (Chargé de recherche, CR) and associate	4
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	8
<b>Subtotal permanent personnel in active employment</b>	<b>23</b>
Non-permanent teacher-researchers, researchers and associates	10
Non-permanent research supporting personnel (PAR)	2
Post-docs	0
PhD Students	7
<b>Subtotal non-permanent personnel</b>	<b>19</b>
<b>Total</b>	<b>42</b>

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: NON-TUTORSHIP EMPLOYERS ARE GROUPED UNDER THE HEADING "OTHERS".

Employer	EC	C	PAR
CNRS	0	3	8
Université d'Orléans	9	0	0
CHR Orléans	0	3	0
<b>Total</b>	<b>9</b>	<b>6</b>	<b>8</b>

## UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	963
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, I-site, CPER, territorial authorities, etc.)	1 696
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	975
Own resources obtained from international call for projects (total over 6 years of sums obtained)	1 315
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	850
<b>Total in euros (k€)</b>	<b>5 799</b>

## GLOBAL ASSESSMENT

INEM is a research unit bringing together immunologists and neurobiologists in two teams, located in the research campus of the university of Orléans. INEM is strongly embedded in the local and regional research tissue and participates in decisions giving impulses and directions to its development, mainly through members of team 1. During the period under evaluation, INEM has globally been very productive as measured in publications, and very successful in acquiring funding. INEM scientists have also succeeded in raising the quality of research output and publications. However, both the productivity and the success in fund-raising differ strikingly between the teams, resulting from the lack of tenured full-time scientists in team 2 which should continue efforts to attract such staff. Moreover, although the committee acknowledged some success in increasing the quality of publications, it considered that both teams could still gain by stronger focusing on a reduced number of topics, and potentially also by increasing inter-team collaboration. The committee noted that the same advice was already expressed in previous Hcéres evaluations of INEM. The committee assesses INEM globally as a very good to excellent research unit, with the potential to advance to an uniform excellent level. The committee noted the strong support of CNRS for the development of an additional research axis on microbiota and pathophysiology in the unit, taking advantage on the unique resources from the TAAM service unit, anticipating a national impact of this research activity. The committee encourages INEM to continue and increase efforts to attract qualified scientists able to develop this axis in close collaboration with the present INEM members. Finally, the committee understands that the leaders of both teams will be replaced by younger colleagues and encourages the current leaders to train and help the younger colleagues to ensure a smooth transition.

## DETAILED EVALUATION OF THE UNIT

### A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Following the encouragement to reach for publications in high-profile journals, the unit could publish 10 papers with senior INEM authors in high-profile journals, compared to 5 in the previous period. Including collaborations, 30 papers also in high-profile journals were published. In addition, 8 papers were signed by members of both teams, attesting effective collaboration.

Responding to the advice of better focusing on a limited number of scientific subjects, the unit focused on sterile inflammation.

The website was updated as requested.

Collaborations with the private sector were maintained, including with ArtINEM.

The unit recruited 11 postdocs, 9 of them from abroad including 8 staying for more than 1 year.

### B – EVALUATION AREAS

#### EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

##### Assessment on the unit's resources

The assessment on the unit's resources is excellent in terms of staff support and funding.

##### Assessment on the scientific objectives of the unit

The assessment on the scientific objectives is very good to excellent. The unit covers historical topics and develops emerging transversal ones, yet the unit would gain from concentrating on fewer research avenues.

##### Assessment on the functioning of the unit

The assessment on the functioning of the unit is excellent.

*1/ The unit has resources that are suited to its activity profile and research environment.*

#### Strengths and possibilities linked to the context

Four main missions have been defined in the unit.

1) Fundamental knowledge on disease pathophysiology and their pathogenic immunological and neuro-inflammatory mechanisms. The research activities are conducted by the 2 teams, whose topics combine inflammation (lung, microbiota), neuro-inflammation, neurotoxicity induced by different environmental cues (pesticides, radiofrequency exposure, several pollutants, herbicides) in several physiopathological conditions: asthma, colitis, bacterial infections, glioblastoma and fragile X syndrome.

2) The unit has a collection of models to transfer their knowledge and test drug candidates. The models include human microbiota transfer, autophagy, a papain-induced asthma model, a model for fragile X syndrome,

bacterial infection, as well as environmental models including cigarette smoke-induced lung inflammation and airway exposure to ozone. They also dispose of *in vitro* models such as neural and human glioblastoma stem cells. These models are partly already used to test drug candidates like for example specific microbiota or metabolites (team 1) and a BKCa channel opener (team 2) for therapeutic or preventive purposes. The KAERUS company has been created in 2016 to develop drugs for the treatment of Fragile X syndrome.

3) The unit is highly involved in university teaching from licence to master levels. They are also involved in the doctoral school for PhD students of the Faculty of Science. The unit supervised 20 PhD students and 140 trainees (from all levels: BTS, IUT, master 2 students). They also open their doors to youngsters at college and high school level.

4) To impact the socio-economic environment and creating job opportunities, the unit has a strong experience in working with the pharma industry and the hospital. In 2016, they created a joint laboratory "Artinem", by combining the private company Artimmune SAS with the unit members. They contribute to the Biopharmaceutical research program of the region Val de Loire, developing several projects and a patent in 2020. They are now part of the Technology Transfer 'TT Booster' program of Orleans- Centre Val de Loire Technopole Lab'O (VQ, BR). After patenting in the area of fragile X syndrome, the first CNRS orphan drug declaration was obtained by one of the team, and the start-up KAERUS has been created in 2016 to set up a clinical trial.

The staff of the unit is composed of researchers affiliated to the CNRS, lecturers from the university and practitioners from the hospital.

The recurring resources come from the CNRS and the university of Orléans. Besides, the members obtain funds for specific research projects, equipment and human resources, of about 82% of the overall budget, corresponding to 4.8 M€ for 2016 to 2021, between 600 to 1000 k€ /year.

Recurrent funds are used for the general organization of the unit (administration, fluids, quality audit expenses, maintenance of equipment, informatics, internal invoices) and also to cover student fellowships, travel or specific costs of the groups. The infrastructure costs are covered by direct recurrent CNRS fundings. Part of the contract funding (5%) is used for general actions and for the funding of the 2 start-up structures. These points are discussed in the unit council meeting. The unit also financially encourages joint projects, transversal ones, ensures continuity in the resources and promotes the emergence of new projects.

The scientific missions of the unit are compatible with the facilities and equipment available on site. The TAAM UAR44 Service is on site. The unit is equipped with L2 labs for human cell cultures, fully equipped for histopathology and haematology, molecular biology, flow cytometry analyses, microscopy, plethysmography for lung function, and devices for ozone or cigarette smoke exposure or behavior studies.

When the resources are not available in house, researchers collaborate with other platforms or externalize services. They run a transcriptomic/genomic/NGS Genotrans platform (CNRS-UniO-CHRO) at the local hospital, and they contribute to a platform at CBM on CNRS campus for cell cytometry and confocal microscopy activities.

## Weaknesses and risks linked to the context

The A2 facility is under refurbishment since mid-2019, it is planned to be re-opened in 2023. One major consequence is that the use of infectious models has been stopped, which postpones some of the scientific objectives of the team like the so-called "Immune responses to infection and injury" project.

Team 1 is far more active in obtaining fundings than team 2: 76% of the projects are funded by team 1 versus 24% by team 2.

*2/ The unit has set itself scientific objectives, including the forward-looking aspect of its policy.*

## Strengths and possibilities linked to the context

One strength of the unit is its historical positioning in advancing fundamental knowledge on disease pathophysiology, especially related to immune responses to infections and pollutants, on neurogenetics and on developmental neurotoxicology. This strategy unfolds in three steps: (i) investigating the molecular mechanisms of human disease pathogenesis, (ii) identifying and validating therapeutic targets using preclinical models and patient derived materials and (iii) developing diagnostic tools. A second strength



opening multiple opportunities are the strong links that the unit has fostered over the years with pharma industries.

New opportunities for the unit are the development of a novel transversal research theme in neuroimmunology and neuroinflammation and the recent arrival of a new Professor in immunology which has allowed the emergence of the allergy topic in the unit.

Concerning the forward-looking unit policy, one strength is the proposed study of exposome and microbiota effects on immune responses and neuromodulation. The attractive opportunity to invest in the "microbiota & inflammation" topic in concert with UAR TAAM is fully supported by CNRS.

### Weaknesses and risks linked to the context

One potential weakness is the lack of clarity on the fundamental and translational questions that the unit wants to address. Indeed, the unit presents its research strategy as a contribution to the following translational challenges: asthma and lung pathology, neuropathology, tuberculosis, inflammatory and infectious diseases. It is not evident that the unit has sufficient resources to address this list of scientific issues, be it at the fundamental or translational levels.

Although re-focusing the research topics has been improved in frame with the previous Hcéres recommendations, it is still noticeable that too many research objectives are pursued given the workforce and resources available. The unit could gain in visibility and impact by concentrating its forces on fewer and relevant topics. Concerning the forward-looking policy, CNRS INSB opened a campaign last year to attract qualified candidates for leading new group(s) around the topic of microbiota and inflammation. Given the strong support of CNRS for this perspective and the attractive local setting close to the TAAM, the campaign will be reopened this year, although in a context of strong competition and several leading positions opened in this field.

### *3/ The functioning of the unit complies with the regulations on human resources management, safety, the environment and the protection of scientific assets.*

### Strengths and possibilities linked to the context

The INEM has implemented specific and relevant actions to comply with regulations in terms of human resources management, psychosocial risks, parity, safety, environment and protection of scientific heritage. There is a good gender balance even though most PhD students were women while 75% of postdoctoral fellows on contract were men.

The administrative tasks under the responsibility of the director are assigned to one secretary and since 2019, an administrative position is mutualized with the CNRS delegation regional. Two prevention assistants monitor health, safety, and working conditions. The "health and Safety" process supports the ISO9001 criteria: 15 management quality and external/internal audits are performed each year. The director and some colleagues attended trainings concerning psychosocial risks.

One technician is the informatics correspondent for INEM. Computers are encrypted, there is an internal network protected by a firewall and secured by a VPN for external connections. A specific server is dedicated to data storage.

During emergency situations and the lockdown, a business continuity plan (BCP) was deployed mainly to maintain key priority.

### Weaknesses and risks linked to the context

A potential weakness mentioned by the ITA staff during the interview with the committee is the non-compliance with biological and chemical safety rules by some unit members. It is important that all INEM staff be aware of the risks and follow the procedures in place.

## EVALUATION AREA 2: ATTRACTIVENESS

### Assessment on the attractiveness of the unit

The attractiveness of the unit is very good to excellent. The unit benefits from an excellent reputation and recognition in the national and international community through an active participation in congresses and seminar organization. The hosting policy reaches a good level owing to the presence of PhD students, guest researchers (about 40 individuals) and 4 new tenure positions. The unit is also active in raising national and international funds and in the management of equipment and skills.

*1/ The unit has an attractive scientific reputation and contributes to the construction of the European research area.*

#### Strengths and possibilities linked to the context

The unit benefits from an excellent reputation and recognition in the national and international community. Although the pandemic slowed down traveling and exchanges, the unit has an active scientific animation: 140 external seminars organized by INEM in 2016-2021, including 70 with international scientists (50%). Altogether, unit members have presented their research on 60 occasions, including 25 invited of which 18 for congress presentations. A unit scientist participates in the organizing committee of the biannual World Congress of Inflammation, and unit scientists have co-organized four "Le Studium" workshops on diverse topics.

Unit scientists have contributed as guest editors for *PLOS One* and on three occasions for *Frontiers in Immunology*. They have been solicited as reviewers by 30 journals including some high-profile journals such as *Science*, *Nat. Med.* and *Nat. Immunol.* The expertise of unit scientists has been sought by national and European grant agencies such as ERC, MRC, SNF (Switzerland), ANR and IUF. Unit scientists are members of the CNRS scientific commission 27 and of the national university council section 65.

International collaborations include, next to various non-formalized collaborations documented through joint publications, a past International CNRS laboratory with South Africa focusing on TB Immunity then continued through a Hubert Curien partnership grant (Protea, 2019-22) and a Marie Curie EU fellowship, and with São Paulo in Brazil (Immune Response and Danger Signals, 2019-2023). While these collaborations involve mainly Team 1, an international laboratory bringing together Team 2 with an Australian group is under consideration.

#### Weaknesses and risks linked to the context

Concerning the construction of the European Research Area, the committee noted that the unit has not been able to exploit its excellent reputation to construct EU-funded network or training projects.

*2/ The unit is attractive for the quality of its staff hosting policy.*

#### Strengths and possibilities linked to the context

The unit has attracted 20 PhD students including 10 having obtained their master outside of Orléans. Among these, some had the opportunity to participate in exchanges in the context of the CNRS International Laboratory with São Paulo (8 laboratory staff involved, including PhD students, Erasmus students and engineers). Results produced by PhD students were presented in 42 meetings although only 13 of these were actually attended by the students. PhD students signed on average 4.7 articles.

The unit hosted a total of 12 guest researchers including postdocs and senior scientists, with many of them hosted by Le Studium, a regional institution designed for hosting visiting scientists during one year-stays and for fostering scientific exchange, or funded by the European Erasmus program. The unit attracted 37 young scientists applying for tenured CNRS or university positions (although many among them had no previous connection with the unit), 4 of them have been successful (1 CNRS, 3 university of Orléans).

## Weaknesses and risks linked to the context

Although PhD projects were presented at numerous meetings, less than one out of three presentations were done by or in the presence of the student concerned. This suggests that some students never had the opportunity to present their data at a meeting during their thesis. As the unit has 13 members habilitated to supervise PhD students, including 3 emeritus colleagues, the number of students (20 in 2016-2021) could be increased. The number of postdocs seems limited, no postdocs were present in the unit starting 2020.

Team 2 has not succeeded in attracting a tenured full-time CNRS or Inserm scientist. Neither, the unit has not been able to identify and attract high-quality candidates to lead the projected third team.

*3/ The unit is attractive because of the recognition gained through its success in competitive calls for projects.*

## Strengths and possibilities linked to the context

The unit obtains 82% of its budget, nearly 5 M€ raised, through competitive national and international calls. The unit obtained the renewal of the IRP (International Research Project) structure with Brasil (82 k€) and 2 projects, coordinated by the unit, with the US (FRAXA Research Foundation USA project) and Australia (Australian Research Council). Finally, the unit has obtained several European programs helping regional development, such as the FEDER: 5 contracts of this type have been obtained for a total amount of nearly 2 M€.

At the national level, the unit contributes from two PIA projects presented by the university of Orléans (Minerve, granted) and the university of Tours (Loire Val Tech, re-submitted). Altogether, the regional authorities funded 11 contracts for a total of 1.5 M€. The other national funds are divided between ANR contracts (7 contracts, 4 of which are led by the unit) for a budget of 140 k€ on average per contract. An application for an "Équipe FRM" grant (2020-2023) was successful (300 k€).

About 30% of the third-party budget obtained has been devoted to pay salaries of young staff on fixed-term contracts, including 7 postdocs, 10 engineers and 2 technicians.

## Weaknesses and risks linked to the context

There is an important imbalance in funding acquisition between the two teams.

*4/ The unit is attractive for the quality of its major equipment and technological skills.*

## Strengths and possibilities linked to the context

The proximity of INEM to the TAAM CNRS UAR44 is a major asset of the unit. TAAM not only provides genetic models and monitoring of health status, but also offers germ-free an A2 facility (though this is presently inaccessible since being refurbished).

The unit has access to standard equipment for histopathology, molecular biology, flow cytometry and microscopy and to more specialized equipment including plethysmography and devices for murine ozone and smoke exposure. The unit also runs a genomic/NGS platform and has access to additional recent NGS equipment in a hospital platform. Additional platforms are accessible off-site, e.g. national sites for computational biology, single cell RNAseq and epigenetic analyses in Tours and Paris, metabolomics (Tours) and mass spectrometry for proteomics (Tours and Orléans).

INEM has set-up a Quality management system monitoring equipment maintenance. Six CNRS technical staff run the equipment at INEM.

The relationship between the Neurogenetics Team and the regional hospital will be extended thanks to the acquisition of recent NGS technology at the hospital platform. Moreover, a biology interface platform "PRIMMO" is in the process of being created at the hospital that will foster interaction between the hospital and local research units. The decision of the national government to create a Faculty of Medicine and thereby convert the regional hospital to a university hospital will provide an important boost to research with medical implications in the environment and the unit.

## Weaknesses and risks linked to the context

Many key platforms (proteomics, metabolomics, single cell RNAseq) are not accessible at ease for unit members, slowing down research projects. Moreover, no dedicated support offering computational biology services has been identified by the committee. This context might be a handicap for competitive research in the current period of big data omics. Lack of access to the TAAM A2 facility during construction and refurbishing work is likely to hamper research of Team 1 relying on infection models.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

### Assessment on the scientific production of the unit

The scientific production the unit is very good to excellent since about 170 publications are documented, although a discrepancy is noted between the two teams.

*1 / The scientific production of the team meets quality criteria.*

### Strengths and possibilities linked to the context

The academic research activity of the unit aims to advance fundamental knowledge in 2 scientific domains, immunological and inflammatory responses as well as neuropathological mechanisms. Consequently, the combined competences are in place to develop original and transversal projects in neuro-inflammation.

The scientific production of the unit is excellent with 154 articles published, 30 of which are in leading specialist journals (*Nature Com, Trends Immunol, JACI*). A total number of 20 reviews have also been published. Among the scientific articles, 59 are led by a member of the unit and 8 are co-authored by both teams. It should be noted that collaborative work is also published in the best specialized journals (*Nature Immunol, Science Immunol*) and that the average number of articles published per PhD student is 4.7.

### Weaknesses and risks linked to the context

There is a large discrepancy in terms of scientific production between both teams. Team 1 published 132 papers during the period, while team 2 published 22 papers since 2016.

*2 / Scientific production is proportionate to the research potential of the unit and shared out between its personnel.*

### Strengths and possibilities linked to the context

The scientific production reflects the research potential of the two constituting teams. It does not sacrifice research quality in favor of quantity, as multiple papers have been published in high-profile journals. The scientific production is imbalanced between the 2 teams, team 1 being more active than team 2. Several reasons explain this situation: all members of team 2 (5 MCF, 2 PR, 1 PH, 2 2 CR/IH) have a large charge of teaching and contribute in clinical practice especially during the covid pandemic. Interestingly, team 1 created the start-up Kaerus biotech to implement a clinical trial, but preventing publication of related results due to embargo from the investors.

### Weaknesses and risks linked to the context

The high imbalance between the 2 teams is directly linked to the researcher composition: 3 full time CNRS researchers in team 1, while team 2 is only composed of researchers with university teaching and/or hospital service duties, and therefore less time dedicated to research.

### 3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science.

#### Strengths and possibilities linked to the context

Concerning data traceability, INEM has a shared and centralized data storage and archiving network, for internal use. INEM developed an independent Quality LRQA Certification upgraded to ISO9001: 2015 and renewed in 2021, to ensure a professional environment, with one internal CNRS audit and one LRQA audit per year. Manuscript signatures are decided within teams.

All experiments comply with the French Government regulations and ARRIVE guidelines. Persons from INEM actively participate to different relevant committees, as the "Ethics Committee of CNRS Campus Orléans" (CCO).

Regarding ethical rules for experimentation with human material and probands, the unit projects comply with the General Data Protection Regulation (RGPD). Members of the unit participate to the hospital's research committee, where the scientific and ethical considerations of each project are discussed. Of note, the Orléans hospital has subscribed to the MR001 and MR003 reference methodologies. Each research project involving patients as well as the relevant consent forms are submitted to a committee for the protection of persons (CPP). Notification of the CPP's favorable opinion is sent to the study investigator and the competent authority.

Projects are verified to be in accordance with the provisions concerning the confidentiality of data to which the persons in charge of quality control of biomedical research have access (article L.1121-3 of the Public Health Code), and in accordance with the provisions relating to the confidentiality of information concerning in particular the nature of the product administrated, the tests performed, the participant people and the results obtained (article R. 5121-13 of the public health code). The persons having direct access to the data take all the necessary precautions to ensure the confidentiality of information related to the products, the identity of the individuals included in the project and the management of the results obtained. An unit Data Management Plan, created thanks to DMP OPIDoR, has been initiated. A meeting with the person responsible for Open Science policy at the university of Orleans has been organized. The unit has created a HAL collection of INEM publications, accessible through the websites of INEM and of the university to improve open publication of research data.

#### Weaknesses and risks linked to the context

None.

## EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

### Assessment on the inclusion of the unit's research in society

The interaction of the unit with the society is excellent and with the economic sector is of outstanding quality.

### 1/ The unit stands out by the quality of its non-academic interactions.

#### Strengths and possibilities linked to the context

INEM is engaged in nonacademic partnerships to develop new therapeutic approaches. The dual expertise of the teams allows the development of transversal research in Neuroimmunology. From "bench to bed" but also "bed to bench" approaches are developed with projects based on *in vivo* functional analysis of genetically modified models. Validation of novel biomarkers can lead to future diagnostic tools.

INEM is part of the FHU HUGO GenOmeds "Génétique omiques médecine et société" granted by Hôpitaux Universitaires du Grand Ouest.

#### Weaknesses and risks linked to the context

INEM scientists including members of team 2 have been involved in only a few clinical trials.

## 2/ The unit develops products for the socio-economic world.

### Strengths and possibilities linked to the context

INEM has been successful in transferring academic knowledge to socio-economic structures: it interacts with private companies (Prodigest, Danone, Boehringer, Novartis) and it has developed and protected intellectual property with 2 patents: KAERUS in 2016 and an European patent in 2021.

Three structures were created and renewed during the period under evaluation. Artimmune SAS was created in 2010 and renewed in 2021 for 5 years (26 joint publications). Moreover, the joined laboratory ARTINEM, between by Artimmune and INEM, and devoted to study the molecular mechanisms of allergic asthma & lung fibrosis was implemented. In 2016, KAERUS biotech was created to develop a novel treatment for fragile X syndrome; a planned clinical phase I trial was postponed due to the covid pandemic. Total fundings from private industry amount is around 850k€.

The teams contributed to the Biopharmaceutical Research Program in the region Centre Val de Loire with the project Bio-Model (2018-2021), filed a patent in 2020 and obtained a maturation project "Pulmo-Protect". INEM is member of the 'TT Booster' program of Orleans Centre Val de Loire Technopole lab'O.

### Weaknesses and risks linked to the context

Despite multiple interactions with large pharma and local biotech, no Cifre contract has been established.

## 3/ The unit shares its knowledge with the general public and takes part in debates in society.

### Strengths and possibilities linked to the context

INEM contributes to different public manifestations through meetings with patients' associations, media discussions, conferences, "Fête de la science", local & regional newspapers. The web site has been improved to provide more visibility of the unit to scientific partners and the general public.

### Weaknesses and risks linked to the context

No weakness regarding this criterion has been identified.

## C – RECOMMENDATIONS TO THE UNIT

### Recommendations regarding the Evaluation Area 1: Profile, resources and organisation of the unit

A tenured research position in team 2 might increase success in funding acquisition and consequently publications of this team.

Since many omics analyses are planned in the future, it might be critical to hire a bioinformatician able to treat the vast amount of data, independently from the collaborations performing the omics studies.

Many research topics are covered by the unit and the jury recommends to increase the focus on few strategical areas of research, concentrating the workforce and the resources on these topics. The jury recommends that a Scientific Advisory Board is setup to advise the unit direction on the most promising topics it should concentrate on.

In order to make the teams members aware of the hygiene and safety rules, it is recommended to provide a regular point of discussion during the laboratory council agenda, as well as quality management organization.

Regarding the administrative tasks supported by the technical staff, the jury proposes to implement "un tableau de répartition des tâches" for a better organization of duties and responsibilities, and to involve both tenured and technical staff on fixed term contracts in administrative tasks.

## Recommendations regarding the Evaluation Area 2: Attractiveness

The jury encourages strongly the unit to increase its efforts to identify and attract qualified researchers as leaders of the third team to develop the research axis of microbiota and pathophysiology. Such efforts may be able to benefit from the strong strategic support of CNRS through a CPJ position (to be reopened in 2024) and the potential opening of a dedicated DR position.

## Recommendations regarding Evaluation Area 3: Scientific Production

There is a large discrepancy in terms of scientific production between the two teams. A tenured research position in team 2 might favor fundings and consequently publications of this team and therefore leverage the scientific production of this team.

## Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

The jury encourages the unit to try and obtain Cifre contracts in the context of its collaboration with ArtImmune, Kaerus and large pharma companies.

INEM could also increase its translational activity through a more active participation in clinical trials.



## TEAM-BY-TEAM ASSESSMENT

**Team 1:** Immune responses to infection and pollutants  
 Name of the supervisors: Ms Isabelle Couillin & Ms Valérie Quesniaux

### THEMES OF THE TEAM

The research topics of team 1 primarily focuses on the immune responses to infection and pollutants. Specifically, the team studies the role of cell death and DNA release as danger signals, as well as type 1 Interferon response in sterile lung inflammation. The research topic "microbiota and inflammation" is emerging in the team through projects dealing with the impact of perinatal or adult microbiota colonization on the immune system. Beyond these main topics the team also study the links between iron and inflammation and continues its past activity about deconstructing the role and cellular sources of TNF/TNFR molecular forms in host response to mycobacterial infection. The team has also developed during the period a transversal axis in collaboration with team 2 focusing on neuro-inflammation. More specifically, this axis aims to decipher some new roles of acetylcholine together with the molecular mechanisms of cerebral malaria.

### CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team successfully had implemented actions to address the recommendations from the previous report.

The team has published regularly in very visible journals, produced joint publications with the other team of the unit and attracted 13 postdocs and guests scientists in the period.

### WORKFORCE OF THE TEAM

<b>Permanent personnel in active employment</b>	
Professors and associate professors	2
Lecturer and associate lecturer	1
Senior scientist (Directeur de recherche, DR) and associate	2
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	5
<b>Subtotal permanent personnel in active employment</b>	<b>11</b>
Non-permanent teacher-researchers, researchers and associates	7
Non-permanent research supporting personnel (PAR)	2
Post-docs	0
PhD Students	4
<b>Subtotal non-permanent personnel</b>	<b>13</b>
<b>Total</b>	<b>24</b>



## EVALUATION

### Overall assessment of the team

The team 1 is overall excellent. It is well structured and attractive, the productivity is high and visible, the finances are solid and diversified and the contribution of the team to the society is very strong.

### Strengths and possibilities linked to the context

The team is large with ample permanent scientific staff: 3 CNRS researchers (2 DR, 1 CR), 2 university professors, 1 *maître de conférences des universités* as well as two emeritus members (1 professor and 1 research director). In addition, the team is well supported with 5 technical staff. The team is divided in 2 groups: "Inflammation, danger signals, infection and lung pathologies" led by a PI DR CNRS and the "Allergy, lung infection and immunity" group led by unit director (DR CNRS). The team has attracted 13 PhD (5 international) and 7 post-docs (5 international) in the period. Of note, the team has recruited a new immunology professor on a permanent position in the period (2020) as well as a CRCN CNRS (2018).

The team is very proactive in its financing strategy through ANR (6 contracts: 3 as PI, 3 as partner; on average 140 k€ per project), FEDER (4 contracts, total 1.65 M€), FRM (label équipe, PI Quesniaux, 300 k€) and private contracts (5, total 560 k€). The team also secured one CNRS international laboratory (82 k€), one PIA maturation contract (210 k€) and the common lab between the team and a company has been renewed (224 k€). In addition, the team is strongly supported by the "Collectivités territoriales" with 11 contracts (1.5M€) and 4 PhD fellowships.

The scientific production is regular. The team has published 132 articles which overall are very well recognized and cited by the community including 28 articles published in leading journals among which 9 are signed by Team 1's senior scientist as lead author. Of note, 80% of the Team 1's publications are co-signed with international collaborators. All tenured scientists of the team publish and the average production of PhD students is 5 articles per thesis including first author publications. One patent has been deposited in 2020.

The team is strongly engaged with the private sector with a spin-off company created in 2010 and a CNRS common laboratory created in 2016 and renewed in 2021 for 5 years. The team also develops strong connections with the Biotechnocentre of the region Centre Val de Loire.

The team is regularly engaged in public outreach via CNRS and INSB communication services as well as CNRS "Rencontres Innovation". The team contributed to media discussions on asthma and malaria, participates regularly to the "Fête de la Science". Of note, the team reports good connections with local politician of the region.

### Weaknesses and risks linked to the context

There is an age and maturity gap between the current management of the team and the newly arrived researchers.

## RECOMMENDATIONS TO THE TEAM

The future management team composition shall take the age pyramid into account in order to foster the emergence of new leaders and the departure of the senior members of the team. The emerging leaders shall be trained and helped in their new role by senior members. Given a specific issue regarding career management in the team, progress reports and open discussion of career choices should be more regularly discussed within the team and with the INEM direction.

To support an increased impact of the deliverables of the team (i.e. publications) and foster further success to competitive grant calls, the committee recommends the team to further integrate in their historical experimental approaches, the great tools they have access at the TAAM. These include gnotobiotic and genetically engineered models, in order to develop large scale "omics" phenotyping, which would be followed by targeted molecular and cellular descriptions.

The committee also recommends the team to concentrate its research efforts on fewer topics and nucleate its workforce and resources in order to support an increased ambition in the quality and impact of research results as well as to enhance fostering links and collaboration with Team 2 especially on the neuro-inflammation topic.

**Team 2:** Neurogenetics and developmental neurotoxicology

Name of the supervisors: Mr Stéphane Mortaud & Mr Sylvain Briault

## THEMES OF THE TEAM

The team domains concern genetic alterations impacting the neurological system leading to intellectual disability and the neurotoxicity induced by different environmental cues.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Following the encouragement to promote its visibility at the international level, the team published 9 articles (among 22) with international collaborators and contributed to 17 communications at international meetings.

Regarding the interactions with the society, the Neurogenetic Team develops several outstanding initiatives to sensitize the general public and teachers to recent advances in scientific knowledge in Neuroscience such as the creation of the 'Neuromyths' escape game, the publication of an illustrated book and teaching kit, and the participation to interactive exhibition conferences and to debates with a public audience.

According to the recommendation concerning the recruitment of full-time researcher, the team recruited a CR1 CNRS in 2018 who however retired in 2021.

## WORKFORCE OF THE TEAM

<b>Permanent personnel in active employment</b>	
Professors and associate professors	1
Lecturer and associate lecturer	5
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	3
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
<b>Subtotal permanent personnel in active employment</b>	<b>10</b>
Non-permanent teacher-researchers, researchers and associates	3
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	3
<b>Subtotal non-permanent personnel</b>	<b>6</b>
<b>Total</b>	<b>16</b>

## EVALUATION

### Overall assessment of the team

The team 2 is overall very good. Its members have been successful in coupling academic research at the fundamental scientific level and translational research leading to innovation and valorized intellectual property.

### Strengths and possibilities linked to the context

The team "Neurogenetics and developmental neurotoxicology" is organized in two groups: group 1 aims to investigate the neurotoxicity induced by different environmental cues (pesticides, radiofrequency exposure, several pollutants, herbicides) and group 2 aims to investigate the physiopathology of Fragile X syndrome (FXS) and to identify new therapeutic strategies. During the evaluation period, group1 showed that *in vivo* (during the prenatal period) or *in vitro* (model of neural stem cell) the exposure to pesticides (CYP and BMAA), herbicides (GLA, PPO) or radiofrequency electromagnetic fields alter neural neogenesis. They also investigated the mechanisms of neuropathy induction via a cocktail of pollutants in interaction with neuroinflammation.

After discovering the role of the BKCa channel in FXS, the group 2 identified visual sensorial deficits of peripheral origin both in the *Fmr1<sup>-/-</sup>* model of FXS and in patients.

The scientific production of the Neurogenetics team in 2016-2021 comprises 22 articles including 13 signed as senior last authors in good specialized journals in the field of neurosciences and toxicology (*J. Neuroimmunol*, *J. Neuro. Dev. Disord*, *Neurotoxicology*, etc.). 5 publications were co-signed by group1 and group2 members attesting internal collaborations. This scientific production is in accordance with team funding and composition. Indeed, the team neurogenetic comprises exclusively personal from the university of Orleans (6 + 1 support) and Hospital (3 + 1 support) with less than 50% effort devoted to research. Team 2 recruited in 2018 one full time researcher who retired in 2021.

The team "Neurogenetics" comprises 6 scientists with HDR authorized to supervise doctoral work. From the 7 PhD students supervised (5 french), four theses have been defended during the evaluated period, with publications in good journals. They are first authors of their main publication and the average production is a 3.5 scientific articles per thesis. The follow-up after the PhD defense shows that most of them are well integrated at national level in the research community. Two post-docs were hosted during the assessment period in Team 2. The team is actively involved in university teaching at all levels of license and master courses.

Team 2 has a good capacity to attract funding (1151 K€ from 2016-2021). Members of team 2 have coordinated 2 international projects (US FRAXA foundation and Australian Research Council Discovery Project) and have participated to 2 other European contracts (FEDER). At the national level, team 2 has coordinated an ANR grant and has also received funding from the local community and private companies.

The medical background of the Neurogenetic Team members and the strong link of the team with the hospital favored the transfer of academic knowledge to the clinic. After patenting in the area of fragile X syndrome (WO/2013/001412, 3/1/2013), the neurogenetic team developed interactions with Bristol-Myers-Squibbs and this led to the creation of the start-up KAERUS in 2016 to set up a clinical trial for the development of a treatment for fragile X syndrome. The covid pandemic postponed the next steps (phase 1 and 2 clinical trial).

The Neurogenetics Team members contributes actively to knowledge dissemination to the public, including large audience conferences. The team develops outstanding initiatives to sensitize the general public and teachers to recent advances in scientific knowledge in Neuroscience, created the escape game 'Neuromyths', published an illustrated book and a teaching kit, and participated to interactive exhibition conferences and to debates open to the public.

### Weaknesses and risks linked to the context

Most team members have published in good journals in their fields but not in high-profile journals. The number of PhD students, post-docs and technical staff in the team has strongly increased. No permanent CNRS researchers are present after the recent retirement of the only full-time researcher of this team. International activities and visibility could be better.

## RECOMMENDATIONS TO THE TEAM

The team is encouraged to hierarchize its scientific priorities and to focus on a major research axis in order to increase competitiveness in their field and to avoid descriptive studies or merely correlative findings, particularly in the project dealing with the impact of environmental toxins on neurotoxicity.

The team is also encouraged to recruit highly qualified and productive international post-docs and PhD students. The team should be reinforced at least by one full-time researcher (CRCN).

## CONDUCT OF THE INTERVIEWS

### Date

**Start:** February 13<sup>th</sup> of 2023 à 9 am

**End:** February 13<sup>th</sup> of 2023 à 7 pm

**Interview conducted online**

### INTERVIEW SCHEDULE

#### **08h45 – 11h40 Unit presentation**

08h45 – 09h00 Committee introduction  
09h00 – 09h40 Administrative presentation of the unit by the DU  
09h45 – 10h15 Inflammation, danger signals, infection and lung pathologies  
10h20 – 10h40 Allergy, lung infection and immunity  
10h45 – 11h15 Developmental Neurotoxicity  
11h20 – 11h40 Neurogenetics of autism and mental deficiencies

#### **11h45 – 12h30 Debriefing-1 committee**

#### **12h30 - 13h00 Lunch break**

#### **13h00 – 13h40 Meeting with ITA**

#### **13h45 – 14h25 Meeting with researchers**

#### **14h30 – 15h10 Meeting with postdocs and students**

#### **15h15 – 15h45 Meeting with institution representatives: CNRS / Orléans university**

#### **15h50 – 16h10 Debriefing-2 committee**

#### **16h15 – 16h45 Meeting with the unit direction: present and future board**

#### **16h45 – 19h00 Redaction of the final report**

#### **19h00 End of the interview**

## GENERAL OBSERVATIONS OF THE SUPERVISORS

## Le Président

Tél : 02 38 49 47 48 - [secretariat.cabinet@univ-orleans.fr](mailto:secretariat.cabinet@univ-orleans.fr)

*Références à rappeler* : EB/SF/24

*Affaire suivie par* : Pascal BONNET

☎ 02 38 49 25 50 ✉ [vp.cr@univ-orleans.fr](mailto:vp.cr@univ-orleans.fr)

Haut conseil de l'évaluation de la recherche et  
de l'enseignement supérieur (Hcéres)  
Monsieur Éric SAINT-AMAN  
Directeur du département d'évaluation  
de la recherche  
2 rue Albert Einstein  
75013 PARIS

Monsieur le directeur,

L'université d'Orléans souhaite remercier l'ensemble des membres des différents comités d'évaluation du Hcéres, conseillers scientifiques et comités d'experts, pour le temps consacré à l'expertise des bilans des laboratoires de recherche et des fédérations.

Lors des échanges entre les différents comités et les directions des laboratoires, il a été mentionné à plusieurs reprises l'absence d'augmentation des dotations des laboratoires.

Il est important ici de souligner que l'université d'Orléans a traversé de très graves difficultés financières lors du dernier contrat quinquennal (2016-2022) et en particulier la mise en œuvre d'un Plan de Retour à l'Equilibre (PRE) à la demande du Ministère pour faire face à une trésorerie négative (2016).

Par ailleurs, sur la même période, l'université a vécu une hausse de ses effectifs étudiants de plus de 25% alors que sa dotation n'a évolué que de 0,5% par an en moyenne.

Cette situation n'a effectivement pas permis une augmentation du budget consacré à la recherche sur cette période.

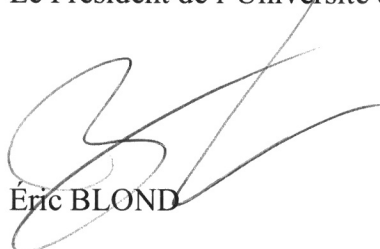
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En outre, cette difficulté financière a également eu un impact sur les recrutements de nouveaux personnels en appui de la recherche, et seuls les départs en retraite ont pu être renouvelés systématiquement.

La situation est assainie depuis 2020 et il est important de noter que les dotations des laboratoires de recherche ont depuis augmenté et que de nouveaux postes de personnels en appui à la recherche ont été créés dans certains laboratoires lors des campagnes 2021 et 2022. Cette dynamique sera maintenue dans les prochaines années.

Je vous prie d'agréer, Monsieur le directeur, l'expression de ma considération distinguée.

Le Président de l'Université d'Orléans

A handwritten signature in black ink, appearing to be 'Eric BLOND', written over the printed name.

Eric BLOND



The Hcéres' evaluation reports are available online:  
[www.hceres.fr](http://www.hceres.fr)

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2 rue Albert Einstein  
75013 Paris, France  
T. 33 (0)1 55 55 60 10

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