

EVALUATION REPORT OF THE UNIT
CEPR - Centre d'étude des pathologies
respiratoires

UNDER THE SUPERVISION OF THE
FOLLOWING ESTABLISHMENTS AND
ORGANISMS:

Université de Tours,
Institut national de la santé et de la recherche
médicale - INSERM

EVALUATION CAMPAIGN 2022-2023
GROUP C

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In the name of the expert committee¹ :

Esther Barreiro, Chairwoman of the committee

For the Hcéres² :

Thierry Coulhon, President

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

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

² 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: Ms Esther Barreiro, Hospital del Mar, UPF, Barcelone, Espagne

Experts: Ms Sylvia Cohen-Kaminsky Centre national de la recherche scientifique - CNRS
Mr Jean-Michel Constantin Sorbonne Université
Mr Mathias Faure Université de Lyon
Ms Grazyna Kwapiszewska Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria
Mr Christophe Leroyer Université de Bretagne Occidentale
Mr Niclas Setterblad Sorbonne Paris Cité

HCÉRES REPRESENTATIVE

Ms Marie-Paule Roth

CHARACTERISATION OF THE UNIT

- Name: Centre d'Etude des Pathologies Respiratoires
- Acronym: CEPR
- Label and number: UMR 1100
- Number of teams: 3
- Composition of the executive team: Mustapha SI-TAHAR

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE6 Physiologie et physiopathologie humaine, vieillissement

THEMES OF THE UNIT

The themes of the unit are

- 1- Infectious diseases, primarily pneumonia caused by the influenza A virus, the Gram+ bacteria *Streptococcus pneumoniae* and the Gram- bacteria *Pseudomonas aeruginosa*;
- 2- Inflammatory aspects of the diseases. The diseases mostly investigated are COPD, idiopathic fibrosis (IPF) and cystic fibrosis (CF).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Research Center for Respiratory Diseases (CEPR) is an academic, multi-team laboratory located in Tours on the shared campus of the faculty of medicine and the Bretonneau University Hospital (CHU). The CEPR was formally and administratively created in 2012 by the INSERM (Institut National de la Santé et de la Recherche Médicale) and the Université de Tours as a continuation/restructuring of Inserm Unit UMRS 618 (Proteases and Pulmonary targeting).

RESEARCH ENVIRONMENT OF THE UNIT

The CEPR is situated in two nearby buildings on the campus and benefits from necessary lab and workspace for its activity as well as efficient access to various technological core facilities on the site as well as vicinity to numerous research laboratories favouring collaborative projects. Teams are interconnected with the Féri regional infectiology network, the regional biology and health network and the 'STUDIUM', a structure aimed at boosting international scientific exchanges in the Centre-Val de Loire region and creating a dynamic scientific community that supports research and innovation. Moreover, they also have strong connections with the MAbImprove laboratory of excellence program, an 'Investment for the Future ('PIA')', the 'Bio3 Institute', a reference platform for training and expertise in the field of bioproduction and the 'ARD Biomédicaments', a regional research cluster that involves academic and industrial partners who work together to advance knowledge on biomedicine and develop innovative therapies.

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

Permanent personnel in active employment	
Professors and associate professors	12
Lecturer and associate lecturer	7
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)	1
Research supporting personnel (PAR)	10
Subtotal permanent personnel in active employment	36
Non-permanent teacher researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	3
Post-docs	3
PhD Students	10
Subtotal non-permanent personnel	18
Total	54

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

Employer	EC	C	PAR
Université de Tours	19	0	8
Inserm	0	6	2
Total	19	6	10

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	1,153
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	1,934
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	2,466
Own resources obtained from international call for projects (total over 6 years of sums obtained)	1,125
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.).	1,165
Total in K€	7,843

GLOBAL ASSESSMENT

The research of CEPR focuses on the understanding of the molecular and cellular mechanisms of inflammatory and infectious respiratory diseases. Specifically, its main themes are: respiratory infection and immunity, proteolytic mechanisms in inflammation, aerosoltherapy and biotherapeutics for respiratory diseases. Each research area is led by a different research team (3 teams, 60 members).

Funding for this period has experienced a significant rise as of 50% greater than that reported in the previous evaluation (€5.3 million during the 2010–2015 period up to €8 million during the 2016–2021). Grant funding represents 85% of the total amount, whereas the institutional amount represents only 15%. The Unit has obtained resources at the national (5 ANR projects, 3 as leaders; 3 national PHRC) and international levels (4 European grants, 2 as leaders).

The attractiveness of the CEPR unit is remarkable. The unit has obtained national and international scientific recognition through the active participation in two GDRs (ResaFlu, Lymphocytes T innés) and COST Networks as well as large-scale European Programs. They have demonstrated an outstanding capacity for attracting new researchers: two new permanent Inserm researchers and one clinician-scientist.

The unit benefits from a very well-connected combination of researchers, teacher researchers and clinician-scientists to achieve its objectives. They display research with a strong human health orientation which increases the possibility of being supported by grants. The visibility of unit members is also attested by numerous invitations of CEPR's researchers to present their work at international conferences (EMBO workshop 2019 (UK); IUBMB 2017 (Netherlands); IPS 2017 (Canada); ASMB 2018 (USA-)). They also participate in organisation activities of scientific events at the national and international level. (Conference on Pulmonary infections, joint meeting, 2021; Seventh International Symposium on Kallikreins and Kallikrein-related Peptidases, 2017...)

The policy for scientific integrity and open science is very well considered, organized, and controlled.

The number of publications is outstanding (over 400; 47% as PI) and quite a few of them have been published in leading position in respected journals such as JAMA, Lancet Respir Med, Am J. Resp Crit Care Med, Intensive Care Med, Eur Resp J., Pharmacol Ther, J of controlled release, Plos Biology, Critical Care, Cell Rep. Clinical research has also been successful, as evidenced by the three PHRC (national project for clinician researchers) obtained during the five-year period. Moreover, they published an article based on the patients recruited during the COVID-19 pandemic (J Exp Med). Furthermore, several members of the unit are co-authors of articles in large audience and multidisciplinary journals (Cell, Nat Immunol, NEJM). They also have several joint publications with industrial partners. Importantly, PhD students and early career scientists are first authors in many of the publications. Sixteen students and thirteen postdoctoral fellows were trained in the Unit.

The unit has filed fourteen patents with the support of the University of Tours, and one of these patents has already resulted in a licence agreement with the company. In addition to the company AERO-drug that was created in 2008 by members of the unit, during the last five years two members of the unit (from teams 1 and 3) have co-founded a new company (Cynbiose RESPIRATORY) along with two private partners.

The unit has developed fruitful and long-lasting interactions with private companies, both in the field of therapeutics and mechanical devices. Links with patient associations, organisations of both national and international symposia, have been extensively developed during the period under evaluation. The unit developed original tools for both scientific audience and lay people, such as access-free videos explaining research concepts and findings. The Unit has created a very supportive atmosphere, including that from the local authorities. The development of partnerships with private companies has also been conducted by the unit. Funding was provided by private partners (Hoffman La Roche, Polyphor and Santhera Pharmaceuticals, GenoScience Pharma, Neuprozyme, Boehringer, GSK). Different actions contributed to the dissemination of the Unit work among nonacademic actors.

In conclusion, the three teams are outstanding and share a very complementary expertise. The collaboration between basic scientists and clinicians is extraordinary, which facilitates the translation of the basic research findings into patients and the clinics.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations of the previous report have been taken into account as the unit has made necessary steps to get international recognition and visibility.

They pursued their efforts to publish in multidisciplinary and with a large audience journals and developed successful collaborations which resulted in significant financial support: ERS-Marie Curie, H2020 grants – acronym 'FAIR' –, Erasmus mundus, Studium funding, H2020 ITN T-OP, COST action (ProteoCure), Public-private international cathepsin C consortium (ICat-CC), EuronanoMed (INAT), H2020 – 'FAIR' –, VIB grand Challenge program – 'IBCORI' –.

In addition to being invited or selected to present their work in National and International Conferences – EMBO workshop 2019 (UK), SFI 2021 (France), ERS 2018 (France), EYIM 2018 (France), IUBMB 2017 (Netherlands), IPS 2017 (Canada), ASMB 2018 (USA), FEBS symposium 2018 (Slovenia), they have also co-organized conferences: Inflamed Cells: Latest News From Inside, 2019; 'Novel host- and microbiota-directed strategies for treating respiratory infections', 2020; Conference on Pulmonary infections, joint meeting, 2021, 1st International Symposium on Cathepsin C (ISyCatC), Tours, 2017; Seventh International Symposium on Kallikreins and Kallikrein-related Peptidases, 2017; Proteases and post-translational modifications in human diseases, Mini-Symposium, 2019, ...

B – EVALUATION AREAS

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

Assessment on the unit's resources

The unit has obtained resources at the national (5 ANR, 3 PHRC...) and international levels (4 European grants...).

They have recruited one clinical member and two Inserm researchers. The unit has fully equipped lab space and cutting-edge equipment. The assessment is excellent.

Assessment on the scientific objectives of the unit

The scientific objectives of the three teams are clear for each team. The CEPR is a laboratory that develops a true from bench to bedside approach from the deciphering of molecular and cellular mechanisms to studies and clinical trials with patients. Members of the Unit are recognised as key European leaders in inhalation delivery of biotherapeutics, which is an innovative approach to deliver non-invasively and at reduced costs biotherapeutics to treat respiratory diseases. The assessment on the scientific objective is excellent.

Assessment on the functioning of the unit

The three teams of the unit collaborate in several aspects: publications, attendance to international conferences, invitations to renowned speakers to give talks in the unit and stays abroad of the members of the Unit. They have a well-organized management plan. The Unit is attentive to the working conditions of its staff, their health, safety, and the prevention of psychosocial risks. The assessment for this item is excellent.

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

Strengths and possibilities linked to the context

The unit has an activity profile that corresponds to its missions (biomedical research) and the possibilities allowed by the human resources placed at its disposal by its supervisory authorities: six Inserm researchers (including 2CRCN recruited during the past six years, 9 university assistant professors and professors, 9 university professors/hospital practitioners and 11 engineers/technicians). In line with its activity profile and research environment, the unit has sought to obtain funds in addition to its recurring resources grant. The overall budget of the unit increased by 51%, from €5.3 million during the 2010–2015 period up to €8 million during the 2016–2021 period (86% external funding). The unit pools part of its own funds (half of the recurrent budgets from Inserm and University + 10% on all contracts) to promote collective research activities and the emergence of innovative themes, among other things. The unit ensures that its scientific objectives are compatible with the premises, infrastructure, platforms, equipment, software and documentary resources at its disposal. It has fully equipped lab space and cutting-edge equipment, including a live cell imaging system, a fluorescence microscope, a high-throughput flow cytometry, several HPLC... The unit scientists also have access to technology platforms (microscopy, mass spectrometry ...) at the University.

Weaknesses and risks linked to the context

The unit has no weaknesses with respect to profile, resources, or its research environment.

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

Strengths and possibilities linked to the context

The unit has a clear vision of its research environment and sound knowledge of its actors. It takes account of the policy of its supervisory authorities in matters of research and exploitation of research findings. The CEPR is a laboratory that develops a true from bench to bedside approach from the deciphering of molecular and cellular mechanisms to studies and clinical trials with patients. Members of the Unit are recognised as key European leaders in inhalation delivery of biotherapeutics, which is an innovative approach to deliver non-invasively and at reduced costs biotherapeutics to treat respiratory diseases. Respiratory pathogens account as a major threat in emerging infectious diseases and the CEPR researchers are involved in national and European initiatives to tackle respiratory viruses such as influenza, that are responsible for both seasonal flu and pandemic viral outbreaks. The Unit involves all its staff in defining its policy on research and exploitation of its findings. Technicians who contribute actively to the results are included as co-authors of the publications. All scientists applied to grants and fellowships to secure the funding necessary to develop their programs. The director and deputy-director are helped manage the unit by a steering committee and the laboratory council. Scientific meetings aimed at promoting exchanges and information-sharing within the Unit include a monthly meeting, a scientific retreat one or twice a year and frequent lectures by external guests. The Unit can analyse the socio-economic and societal impacts of the policy it conducts. It has tied strong and long-term partnerships with biotechs, pharmas, and medical device companies. Several of these partnerships have proved fruitful, entailing the acquisition of substantial operational resources (staff, equipment...) as well as patent applications (one licensed to Nemerq). Considering the huge health and economic burden of respiratory disease in particular COPD and respiratory infections, the societal impact of CEPR is obvious and exemplified by various prototypes (nebulizers...) and clinical trials.

Weaknesses and risks linked to the context

The unit has no weaknesses with respect to its scientific objectives, including the forward-looking aspects of its policy.

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 unit complies with principles of human resources management that respect gender equality and are non-discriminatory, in matters of training, internal mobility and career development for its staff. Numerous initiatives have been taken, notably the deployment of an action plan to combat psychosocial risks, the development of teleworking and the implementation of a lab life committee. Job positions are open to male and female, as well as disabled individuals whenever possible. The three teams are headed by one female and two male scientists, but an additional team headed by a female scientist is going to join the CEPR soon. The Unit is attentive to the working conditions of its staff, their health, safety, and the prevention of psychosocial risks. There are three health and safety managers in the Unit. They provide practical training to all newcomers and supervise the implementation of health and safety practices. The unit applies all the necessary provisions for the protection of its scientific assets and computer systems. The unit applies the recommendations on environmental risk prevention and the pursuit of sustainable development goals in accordance with the University of Tours policy (electrical equipment and computers are turned off in the evening, chemical waste and biohazards generated in the lab are collected and taken over through a regulated clearance circuit). The unit regularly updates a business continuity plan (BCP) to enable it to cope with any emergency situations such as the COVID-19 pandemic.

Weaknesses and risks linked to the context

English language should be used more frequently, particularly when PhD students and postdocs present their main research projects. PhD students should participate more in research presentations and particularly in journal club sessions.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the CEPR unit is remarkable. The teams show national competitive (5 ANR, 3 as PI) and international scientific recognition, participating actively to GDR and COST Networks and to major European Programs (Euronanomed, H2020, ERD Marie Curie etc...). They have outstanding capacity of attracting new researchers and were able to recruit new permanent Inserm researchers, lecturers and clinicians. Doctoral students (16 PhD theses defended) and postdoctoral fellows (13 hosted) have many opportunities to improve their skills and thus increase their scientific impact. The policy for scientific integrity and open science is very well considered, organized, and controlled.

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

Members of the unit organized or participated to the scientific committees of ~35 international and European congresses/meetings. These meetings were in general in their area of specialities (Mo Ab for respiratory diseases, kallikreins, cellular proteolysis, aerosol medicine, respiratory research, etc.).

The visibility of unit members is also attested by numerous invitations of CEPR's researchers to present their work/findings in ~50 international reference large-audience congresses/meetings (such as ERS congress, ISAM congress, ATS congress, FEBS and IUBMB meetings, IPS congress, ASMB congress, EMBO workshops...). They were also regularly invited to present their work to renowned international academic institutions (in Germany, UK, Belgium, and Canada) or to private companies (Sanofi, Aerogen). They were actively involved in the creation and national steering committee of the Respirator Research Days J2R, the first meeting being held in Reims in 2005. Importantly, two unit members were chosen to co-organise the '2023 J2R' that will take place in Tours in Oct 2023. This event puts directly and indirectly a great 'light' on the CEPR research activities as well as on its staff members.

In addition to considerably adjusting their publication policy on quality (they produced several publications in large audience journals, including Eur. Respir. J., J. Exp. Med., NEJM, JAMA, Cell, Cell reports, PNAS USA, AJRCCM, Pharmacol Rev.), CEPR members hold editorial responsibilities in many international and national journals, in agreement with their respective expertise. There is namely participation to Scientific reports (Nature group). Moreover, members have succeeded in recruiting researchers with remarkable publication track records (2 publication in Nature, 1 in Nature Microbiology, 1 in ISME Journal, etc.). And that they also have prestigious collaborators with whom they have published studies in renowned generalist journals (Nat Immunol, Eur Resp J., N. Engl J. Med, JAMA, JACC, Lancet Resp Med, Lancet Infect Disease), which also contribute to their exceptional attractiveness. Members of the unit take part in many research steering or scientific expertise bodies at international, European, and national level. Among others, unit members were representative of the French inflammation society at the International association of inflammation societies (IAIS), were remote experts of the H2020-FETOPEN proposals from 2019 to 2021 and are currently experts for EIC-Pathfinders proposals, have also been monitoring the H2020-FETOPEN-1-2016-2017-767015– CURE project (2018–2022). They were also involved as grant evaluators in many Research agencies or foundations in Europe (Poland, Slovenia, Ireland, UK, Italy...)

They participate in numerous research steering committees at the national level (French Ministry of Health, ITMO Technology for Health, HAS, National Research agency ANR, Pasteur Institute staff evaluation committee, National Research Networks GDR ResaFlu GDR Innate T cells. All members are often advised to evaluate national grant applications (ANR, Inserm international research projects, research in respiratory medicine foundation, BPI France, ANSES...).

Awards and prizes at the national and international level mainly include research fellowships, Inserm contract-d'interface, and many best presentation awards (J2R, ATS, ERS, etc.).

Weaknesses and risks linked to the context

In order to improve their national and international recognition and visibility, some senior members of the unit could try to apply for national or international scientific prizes and other distinctions,

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

Strengths and possibilities linked to the context

Doctoral students and postdoctoral fellows have many opportunities to improve their skills and thus increase their impact. They are fully involved in their research projects and benefit from equipment and/or facilities under the supervision of specialised tech staff and mentoring of PIs, thus encouraging responsibility and promoting the performance of their research. They participate in cutting-edge training courses, including to improve transversal skills. They attend competitions such as 'Ma these en 180 sec', as well as conferences and congress awarding, thus encouraging self-improvement. They are also encouraged and trained to participate in funded competitive projects, including the ERC starting grant, ATIP-Avenir, ANR JCJC and Marie-Sklodowska Curie programs), are involved in collaborative projects with private entities (SME or Pharma companies). They actively participate in regular lab meetings as well as in national or international conferences and congresses. They get on a request basis support for English courses to improve their communication skills, training on electronic sources of information. They interact with visiting scientists from other labs and countries. Finally, on a request basis, they can be involved in university teaching experience.

The unit shows remarkable attractiveness to junior and senior researchers who applied for tenured positions. Despite the strong competition for tenure position at Inserm, the CEPR recruited successively two young Inserm research associates (so-called 'CRCN' positions): one in 2020 associated to team 1 and one in 2021 associated to Team 3. One member of team 1 was a laureate of the Maitre de Conference (assistant professor) contest in 2020. Two junior clinicians obtained tenure positions as 'Professor–Hospital practitioners (so-called 'PU-PH'), one in team 1 (2020) and the other in team 3 (2018). Remarkably a researcher with an Inserm 'DR2' position was attracted to join the CEPR in 2023, to take the leadership of the future team 1 (with the support of M. Si-Tahar as a deputy-leader). CEPR is also a favourable environment to promote research carriers to full research professor ('DR'). Young Physicians of the unit were awarded a highly competitive Inserm research fellowship to carry out their PhD training (so-called 'poste d'accueil Inserm') in 2020 and 2016 and 'Contrat d'interface pour hospitaliers' in 2021.

The CEPR has hosted several renowned guest scientists of various nationalities. One of them, from Leiden University medical centre (LUMC, Netherlands) helped team 1 to set up a sophisticated culture model of primary human lung epithelial cells (at the air-liquid interface) as well as organoids, two relevant settings that better mimic the lung mucosa. Several others from Belgium, Germany, Ireland, Brazil, Switzerland, Poland ... but also renown researchers from France (from Bordeaux, Marseille, Paris, Brest, Nice, etc.) became collaborators after scientific seminars.

The policy for scientific integrity and open science is very well taken into account, organized, and controlled, according to the University of Tours and Inserm policy. Any new entrant has to read, validate and sign the research integrity charter, which was included in 2020 to the 'Welcome/Rules of Procedure' booklet of the CEPR. Members of the unit are aware that they can contact the local ethics referents to discuss or receive information. All PhD students attended a mandatory seminar dealing with 'the ethics of research and scientific integrity'. With regard to open Science, the CEPR created a specific HAL portal gathering all the scientific post prints/open access publications of the CEPR, with a yearly update.

Weaknesses and risks linked to the context

No weakness nor any risk could be identified regarding this criterion.

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

Since the last HCERES evaluation and according to the recommendations of the HCERES committee, the unit has made a tremendous effort in increasing its international visibility through major new collaborations, namely at the European level, that also resulted in significant financial support. CEPR is involved, in four European/international collaborations/partnership and initiatives related to respiratory infections and proteolysis, mucosal immunity, and drug delivery by inhalation to treat respiratory diseases, two as coordinators, two as partner and task leader (one as a member of the steering committee).

The unit is moderately involved in structures and projects funded by the Future Investments Programmes (PIA). They participate to the LabEx MAbImprove with team 3, co-leading a research axis and taking part in the steering committee. Over the 2016–2021 period, they were successful in obtaining competitive funding from the National Research Agency (ANR). The unit has coordinated three ANR projects (NKTDiff, SuccesS, COMAIT-19) and has participated in two other ANR projects (NEBUNIPASTOP, SiSHO). They were also successful in other calls for projects issued by the supervisory authorities (French Government Defence procurement and technology agency (DGA-RAPID project Pneumophage). They obtained support for five Clinical Research Programmes either at the national level (n=3) or inter-regional (n=2). Over the 2016–2021 period, the unit also obtained funding from a/the Region Centre Val de Loire either as project coordinator (Novantinh, Mutinh, 7UP, Pirana, FLU-MET) or partner (Exaspir17, BioMind), b/national learned societies/charities (Vaincre la Mucoviscidose, Ligue contre le cancer, Foundation of rare diseases).

Remarkably, the members of the unit (staff of 54, of which 36 are permanent) have raised a total of 7,843 k€ in six years, the highest amounts being for national projects – 2,466 k€, 31% of the total – and regional projects – 1934 k€, 25% of the total –. International projects bring 1125 k€ (15%) and a significant part of the budget also comes from transfer and industrial collaborations (1165 k€, 15%). Compared to that, the recurrent budget represents only 15% of the global budget of the unit (1153 k€).

PIs of the CEPR have thus obtained 85% of their financial needs to ensure the continuation of their research programs, and to cover namely funding of doctoral, postdoctoral as well as tech recruitment, and the purchase of major equipment (e.g., a live cell analysis instrument (Incucyte) for a cost: 160 k€).

Weaknesses and risks linked to the context

While the unit is now well involved in European networks and projects, and obtained five competitive ANR funding, it participates little in national structuring programs such as Future Investments Programmes – PIA –. The presence of many university hospital clinicians is an opportunity to favour the participation of the unit in DHU or IHU programs.

Despite their participation in international projects, the unit didn't take this opportunity to attract international postdocs or PhDs in the unit, which in turn could have a positive impact on the French students and postdocs, through multicultural exposure and immersion in the English language on a daily basis at the Laboratory.

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

Strengths and possibilities linked to the context

The unit benefits from easy access to the expertise and cutting-edge technological resources that make up its immediate environment and from a quality technological environment and is also very well equipped on-site. They also have access to Metabolomics, genomics, microscopy, preclinical imaging, and Cytometry & Single-

cell Immunobiology platforms (the last one taken over by a unit member), that are largely used as shown by the large number of publications citing them. The unit has also developed its own platform for aerosol metrology and deposition, lung models to mimic ventilation and respiratory parameters of patients, and for the use of radionuclides to measure aerosols (in a restricted access area).

The Cytometry & Single-cell Immunobiology platform led by the unit since 2021 is very well equipped with new state-of-the-art instruments, and Université de Tours recently appointed a dedicated research engineer to the platform. These new technologies are very important for the unit projects and for the scientific community in Tours. As for the aerosol metrology platform, it is an important asset for interaction with industrials (pharmas and medical device companies) either as subcontract or collaborations. It is important to note that the lab has been designated by the ANTADIR (Association Nationale pour les Traitements A Domicile/national association for at-home treatment) federation as the national reference centre for the evaluation of nebulizers and inhalation chambers.

On-site platforms are operated by well-trained technicians and engineers employed by the University of Tours who are affected to the various platforms.

Weaknesses and risks linked to the context

No risk identified

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The quality of the scientific production is outstanding with a total of 450 papers. They published 256 original articles including 102 signed in a leading first/last/corresponding position, among which more than 15% in notorious scientific journals. They also published 59 reviews, with 38 in a leading position (30% in high-level journals), and numerous editorials and clinical reports. They actively contributed to collaborative works published in large audience journals as well, pointing further importance of the unit in the international arena.

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

Strengths and possibilities linked to the context

The institute is dedicated to biomedical research and human health and is involved in the entire range of activities from the laboratory work to the patient's bedside which is a clear strength. CEPR has access to three major biobanks ImPACT (Innate Immune Response During Community Acquired Pneumonia), RICEPS (Immune Response Under Immunotherapy in Metastatic NSCLC: Sputum, Blood Samples and Microbiota Study) and UNLOCK (Implication of UNconventional T Lymphocytes in Cystic Fibrosis) which deliver enormous value for the unit.

The number of publications is impressive (over 450 total) and some of them are in respected journals such as ERJ, AJRCCM and AJP-Lung or FASEB J. Publications include basic, translational, and clinical studies conducted by members of the unit, collaborative work and articles by researchers who have recently joined the unit. Importantly, PhD students and early career scientists serve on some of them as first authors, what is a very crucial achievement for their career development. Some members of the unit are co-author of articles in outstanding journals (Cell, Nature, NEJM). There are also several joint publications with industrial partners which strengthen the translational aspect of the conducted research.

The scientific production is of a very good level with more than 65% of publications in speciality journals. The unit benefits from a very well-connected combination of researchers, teacher researchers and clinician-scientists to achieve its objective. They display research with a strong human health orientation which increases the possibility of being supported by grants. The recent recruitment of new investigators will increase opportunities to publish in high impact journals.

Weaknesses and risks linked to the context

The unit has concentrated in publishing their work mostly in speciality journals. There is a low number of papers in high audience journals where the outstanding translational research conducted by this unit should be published, as expected.

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

Team 1 composed of ten PI (3 researchers – 1 DR + 2 CR –, three teacher researchers (MCF), four clinician researchers (3 PU-PH + 1 PH)), five technicians/engineers, four postdocs and nine PhD students has published 196 articles and filed patents.

Team 2 composed of eight PI (1 researcher – CR), six teacher researchers – 2PR + 4 MCF –, 1 clinician researcher – PU-PH –, three technicians/engineers, four postdocs and nine PhD students have published 94 articles and filed four patents.

Team 3 composed of seven PI – 2 researchers (1 DR + 1 CR), five clinician-scientists (4 PU-PH + 1 MCU-PH), five technicians/engineers (1 at 50%), four postdocs and ten PhD students published 158 articles and filed nine patents.

Thus, taking in consideration the staff number, the three teams produced almost a similar quantity of scientific deliverables, with team 2 having only a bit smaller publication number. Nevertheless, the overall scientific production leading to the general output of the institute is distributed equally between the teams. The doctoral and postdoctoral students fairly contribute to the scientific production activity.

Weaknesses and risks linked to the context

Although the quantity and quality of the scientific production is very good, the emphasis might be more directed towards higher audience papers which would lead to increase the visibility of the institution. Taking in consideration the excellent scientific environment and the networking between clinical and basic scientists, the weak point is the lack of translational outstanding papers, where all unit members contribute with the best technologies, combined with existing biobanks and clinical applications. Bringing all combined forces together could lead to publications in journals as Science Translational Medicine, Nature Commun, Cell, etc. where early career members could serve as first authors.

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

The CEPR is involved in all aspects of the scientific integrity process. CEPR trains its permanent and non-permanent staff on good practices in the conduct of research activities in order to obtain flawless results, to guarantee traceability and reproducibility. These means are based on the CNRS Guide on 'integrity and responsibility in research practices' and are part of the training of the PhD students.

Weaknesses and risks linked to the context

None identified.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit develops fruitful and long-lasting interactions with private companies, both in the field of therapeutics and medical devices. Remarkably, over the 2016–2021 period, the unit declared three inventions, filed fourteen patent applications or European/international extensions. Fourteen industrial contracts have been signed. Links with patient associations, and organisation of both national and international symposia, have been extensively developed during the period. The unit developed in addition original tools for both scientific audience or lay people, such as free videos explaining research concepts and findings. The overall assessment of this item is exceptional.

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

Strengths and possibilities linked to the context

Development of partnerships with private companies is conducted by the unit, both to validate research hypotheses and to fasten potential access to innovative therapies. Funding in that instance was provided by private partners. Among the numerous collaborations, took place:

- 1) Evaluation of cathepsin S inhibitor petesicatib (Hoffman La Roche);
- 2) assessment of inhibitory properties of an inhaled neutrophil elastase inhibitor Ionodelestat, including a phase one study in cystic fibrosis patients (Polyphor and Santhera Pharmaceuticals);
- 3) characterisation of a novel autophagy inhibitor therapeutic candidate, a chloroquinone-derived drug identified as a potent anti-fibrotic and pro-fibrolitic agent in liver fibrosis through TGF- β 1 inhibition (GNS561), including a Phase 1b/2 clinical trial (GenoScience Pharma);
- 4) identification of neohesperidin dihydrochalcone (NHDC), a potent, competitive, and selective inhibitor of cathepsin S (LVMH);
- 5) design and evaluation of cathepsin C inhibitors in vitro and in preclinical diseases models (Neuprozyme, Boehringer, GSK);
- 6) analysis of the properties of a lysosomotropic autophagy inhibitor (GNS561), including a Phase 1b/2 clinical trial (GenoScience Pharma).

These partnerships have the potential to make new therapies available for different chronic diseases in the next few years.

Close attention was paid to interactions with patient associations (pulmonary fibrosis (AFPF and Enjalran) and lymphangioliomyomatosis (FLAM)). One member of team 2 is responsible for the 'competence centre for rare pulmonary diseases' and two members of team 1 take part in the activities of 'Vaincre la mucoviscidose' association.

Different actions contributed to the dissemination of the unit work among nonacademic actors: invitations by private partners to give seminars; two organisations of symposia and industrial workshops; several oral communications and lectures to industrial workshops or international congresses with a large non-academic audience; articles in specialised non-academic or professional journals.

Weaknesses and risks linked to the context

Considering both the limited number of permanent staff and the numerous mandatory administrative tasks linked to the nature of the research projects, reinforcement of the team with an administrative position under direct supervision of the unit leaders is welcome.

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

Strengths and possibilities linked to the context

Over the 2016–2021 period, the unit declared three inventions, filed fourteen patent applications or European/international extensions. As an example, for team 3, three patents were co-owned with private partners (Nemera and Sanofi, France; Argenx, Belgium) and three were co-deposited with other academic institutions (INRAe, Institut Pasteur and CNRS; University of Athens). One patent was licensed (Mouthpiece for inhalation licensed to Nemera, France) and two are undergoing maturation stage with private partners.

The leaders of teams 1 and 3 have cofounded a CRO 'Cynbiose Respiratory' with two private partners, with the aim to develop inhaled drugs for respiratory diseases; three people, including one project manager, were recruited. Contribution to the drafting of recommendations or guidelines was also consistent (with Afnor, Antadir, ANSM, the French Ministry of Health, WHO...) as well as contributions to the evaluation of projects at a French level (Anses, ANR, Inserm, BPI France...) or at a European level.

Weaknesses and risks linked to the context

As underlined above, reinforcement of permanent staff might help the unit tackle with the numerous administrative tasks directly linked to this extensive development.

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

Strengths and possibilities linked to the context

Public science activities at the unit level included: talks on Radio RCF, German and Turkish TV channels (on therapeutic targeting of cathepsin C and presentation of clinical trials); interviews for TV programs (Allo Docteurs — France 5 TV in 2016, France 3); conference at the Opéra de Tours, after selection by a popular jury of TEDx (ideas to change the world); organisation of school initiatives for school pupils for the introduction of the world of science with different actors.

Several publications of articles in multidisciplinary general journals devoted to biology, medicine, and health research (Medecine Sciences...) or general public press (Le Figaro...) have been produced at the unit level.

In addition, Team 3 developed videos to explain some research concepts that are accessible on internet. For example, a video was done to explain the Retronose® approach developed with Nemera and a video motion design produced for the VIB Grand Challenge project IBCORI to explain the biological-based solution proposed to control influenza and delivered by inhalation. Team 3 also developed a Website presenting its research, location, key results and Websites presenting the objective, partners, news of some projects, in particular European projects (<https://fair-flagellin.eu/>; <https://vib.be/grand-challenges-program/ibcori>).

Weaknesses and risks linked to the context

No weak point identified.

C – RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

In general, the unit's performance is outstanding. No major weaknesses have been identified regarding Area 1 (profile, resources, and organisation). If any recommendation is to be made, the use of the English language should be improved among all the members of the Unit. PhD students and postdoctoral fellows should be more frequently exposed to presenting their results at international events, where English is the common language. PhD students should also participate in the organisation of the research seminars and journal club sessions.

Recommendations regarding the Evaluation Area 2: Attractiveness

Unit members should further increase their visibility by participating in the organisation of large audience congresses such as ERS and ATS, by participating in speciality assembly at ERS and ATS, they could propose Scientific sessions on their favourite topics. This would create a virtuous circle with a cross-fertilisation on the international visibility of the unit members and of the themes developed in the unit.

Unit members produced several publications in journals of the MDPI and Frontiers series. However, they should try avoiding these publishers and their journals that may be considered in some way predator journals, or at least limit their rate of publication in these journals.

They should increase the number of PhD students.

Recommendations regarding Evaluation Area 3: Scientific Production

Taking in consideration the outstanding performance of the unit, the recommendation would be to aim for publications in the more general top journals such as Nature Communications, Science Translational Medicine, Nature to name a few.

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

The committee recommends to actively pursue fruitful initiatives conducted during this evaluation period.

TEAM-BY-TEAM ASSESSMENT

Team 1: Respiratory infections and immunity
 Name of the supervisor: Mr. Mustapha Si-Tahar

THEMES OF THE TEAM

Team 1 'Respiratory Infections & Immunity' is a multidisciplinary team, conducting fundamental and translational research in the field of host-pathogen interactions. They are focusing their translational research program on understanding the mechanisms underpinning host-pathogen interactions by combining experimental and clinical studies in order to propose innovative strategies to fight lung infections. The team gathers microbiologists, immunologists, and physicians to cover the multi-facets of the host-pathogen interactions:

- 1) Basics on microbial virulent factors;
- 2) basics on the biology of immune cells;
- 3) Analysis of mechanisms associated with the host response in both experimental and clinical studies;
- 4) Proposals of innovative anti-infectious strategies targeting either the pathogen or the host.

Team members are interested to study the biology of key molecular (e.g. metabolites and cytokines) and cellular (e.g. innate-like T lymphocytes, neutrophils, macrophages and epithelial cells) actors of the host immune response to infection in the lung mucosa (Axis 1). In addition, the team has a strong interest in the understanding of the intrinsic factors of pathogens that modulate and/or subvert the host immune response (e.g. virulence factors) or contribute to antimicrobial drug resistance (Axis 2). Altogether, these axes of research aim at paving the way towards innovative treatments that target either the pathogen or the host response.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendation was *'to get international recognition, by not only delivering better publications in higher impact factor journals, but also by spreading the word about such a unique set up. It could be done by organising more international conferences, which is already happening to some extent, by attending major conferences and by getting better exposure through communication on social media.'*

According to this recommendation Team 1 has adjusted its policy of publications by putting a premium on quality. Graphs are presented illustrating a clear rise in their annual publications as compared to the past mandate (2011-15). In addition, the median of annual citations per PI gradually increased since 2016. This Team 1 also increased its international visibility through major new collaborations that also resulted in significant financial support (CoFund ERS-Marie Curie, H2020 grant (acronym 'FAIR'), Erasmus mundus research funding, Studium funding, H2020 ITN T-OP). Unit members were invited or selected to present their research achievements in reputed international meetings: EMBO workshop 2019 (Oxford, UK), SFI 2021 (Paris), ERS 2018 (Paris), EYIM 2018 (Paris). Several members continued to (co)-organise international conferences despite the two years constraints related to the COVID19 crisis (Inflamed Cells: Latest News From Inside, March 2019; 'Novel host- and microbiota-directed strategies for treating respiratory infections', Sept. 2020; Conference on Pulmonary infections, joint meeting 'RSRQ/J2R', May 2021). Efforts were made by team members to bring expertise and scientific activities on social media, including in Twitter, LinkedIn and Youtube.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	3
Lecturer and associate lecturer	3
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	2
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	3
Subtotal permanent personnel in active employment	12
Non-permanent teacher researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	3
Post-docs	3
PhD Students	3
Subtotal non-permanent personnel	10
Total	22

EVALUATION

Overall assessment of the team

The overall assessment of the team is rated outstanding, due to their scientific contribution, originality and impact of results, quality of publications, attractiveness, communication, and transfer to the society. They demonstrated excellent capacity to acquire joint grants and publish with partners of the highest international level. The scientific production is in line with the research potential of the team, and also attested by numerous invitations to present their work in major national and international congresses. All senior researchers and professors are active publishers and the doctoral and postdoctoral students have contributed to this production.

Strengths and possibilities linked to the context

The workforce of Team1 is well balanced between permanent and non-permanent personnel. Regarding research supervision potential, seven of the ten principal investigators have their 'authorisation to direct research ('HDR')'. However only three PhD students are currently recruited, although nine PhD students have been supervised during the year period. This can be explained by the fact that many of these PIs have heavy activities in the administration of research, coordinating networks, coordinating competitive grants, being members of steering committees, evaluation of research committees, etc.

The scientific production of the team is original, and they made a significant contribution to knowledge in their research area, with high-quality research publications in line with their editorial policy. In relation to their axis 1, they have identified several new pathogen-derived factors that influence the host immune response during lung infection, as potential future therapies. They characterised the mechanisms by which these factors regulate the host response. They identified, tested and optimised innovative antimicrobial drugs to target pathogens during lung infections. About ten major publications, one patent and one declaration of invention emerged from this work. With regard to Axis 2, team 1 has identified several immune pathways that control the development and regulation of the host response during lung infections bringing new insights into the pathophysiological processes of pneumonia and its complications. New knowledge on key cellular and molecular actors of the host response

to lung infections emerged from their work. The team also developed several projects aiming at harnessing the immune response during pneumonia in both preclinical and clinical studies/trials. They also took the opportunity of working on Covid19 programs. They published about twelve major papers on this Axis, and participated as promoters to two clinical trials. The results of one of these trials were included into a prospective meta-analysis as part of the REACT working group, to increase statistical power (n = 1703 COVID-19 ICU patients). Importantly, this meta-analysis led to the publication of a guideline from the WHO to use systemic corticosteroids in the treatment of patients with severe COVID-19.

Many of team 1 PIs have activities in the administration of research, coordinating networks, coordinating competitive grants, being members of steering committees, evaluating research committees, etc. Team 1 shows an outstanding research activity. They contributed in total to 196 articles (among which 114 original articles, 45 review/editorial articles, and 37 clinical reports) during the six-year evaluation period, more than 95% of which are categorised of high quality being published in high-reputation journals. Of these 196 articles, 92 (47%) are PDC. The team favoured, when possible high-reputation multidisciplinary journals such as four in PDC (1 JAMA, 1 J Exp Med, 1 Nature Commun, 1 JCI Insights) and 26 as collaborators: *NEJM* (n = 2), *JAMA* (n = 3), *Cell* (n = 1), *J Exp Med* (n = 2), *Nat Commun* (n = 8), *Cell Reports* (n = 6), *PNAS* (n = 2), *JCI Insights* (n = 1) and *JCI* (n = 1). Due to the multidisciplinary nature of the team, the reference journals are different according to the field of interest: a/ Microbiology and antimicrobial strategies: *Nat Microbiol* (n=1, 1 PDC), *Antimicrobial Agents and Chemotherapy* (n=2, 1 PDC), *Antiviral Research* (n=1, not PDC). b/ (Lung) Immunity: *Nat Immunol* (n=1, not PDC), *Immunity* (n=1, not PDC), *Eur Resp J.* (n=3, 1 PDC), *Mucosal immunology* (n=3, 1 PDC). c/ Intensive care medicine: *Intensive care medicine* (n=3, 3 PDC), *Critical Care* (n=4, 2 PDC).

Team1 filed two patents and one declaration of invention, and a Team 1 member cofounded a CRO company named Cynbiose RESPIRATORY based on the transfer of in-house skills, in experimental models of respiratory diseases. Team1 also coordinates a national hospital clinical research project (PHRC) 'CAPE-CODE' and its extension 'CAPE-COVID' to "Study of the effects of low-dose corticosteroid therapy on the evolution of severe acute community-acquired lung diseases (including COVID-19)". They also developed a joint program with Chemineau Labs to set up an innovative treatment of influenzas based on their discoveries.

Weaknesses and risks linked to the context

The team needs to enrich its skills by catching up in bioinformatics analysis. Their broad field of expertise, i.e. bacteriology, virology, immunology, molecular biology and clinics, is both an asset and a risk. Although they are successful in treating a broad range of topics, their research could be more focused in the future. They should put their talents at the service of more focused research in the coming years in order to increase the specificity of their image in the scientific community. As in many research units in France, the lack of permanent technical staff and an unfavourable PI researcher/technical staff ratio can be deplored, which leads to the hiring of temporary staff and does not allow the know-how to be maintained and stabilised within the team.

RECOMMENDATIONS TO THE TEAM

Team 1 is conducting several ambitious Omics projects and should think of securing Bioinformatics/Bioanalysis skills which are already present in the team. Their attractiveness, that they demonstrated brilliantly, should be an asset in doing so. Team1 should try to increase the number of Postdocs and PhD students, as they have the capacity to do so both in terms of supervision potential (7 HDR) and funding raising capability. Moreover, thanks to their international network, they should try to attract and enrol foreign PhDs and postdocs to foster the use of the English language during the training of the students.

Team 2: Proteolytic mechanisms in inflammation
 Name of the supervisor: Mr. Gilles Lalmanach

THEMES OF THE TEAM

Team 2 is a basic research team investigating proteolytic mechanisms associated with two chronic pulmonary diseases (Chronic Obstructive Pulmonary Disease (COPD) and Fibrosis). It also aims to investigate the mechanisms behind targeting, control, and regulation of proteolytic activity using peptide-, pseudopeptide inhibitors or antibodies. Specifically, the team is interested in the involvement of serine proteases such as elastase, cathepsin G and proteases derived from neutrophils and epithelial cells and cysteine cathepsins, derived from fibroblasts and macrophages. Their ultimate goal is to restore the homeostasis of the proteolytic (protease/antiprotease) balance for better treatment of the lung diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The major recommendations from the previous report were

- 1) to concentrate on articles of very high impact factor as first or last author,
- 2) to obtain international (EU) collaborative research contracts, to recruit more foreign postdocs with their own funding and to apply for funding for translational projects from the ANR,
- 3) and to prioritise the projects, based on scientific excellence, specific available resources, and synergies with the other teams in the unit.

Team 2 has tackled those recommendations in the following manner. Members have published numerous articles (94 publications) in well-known journals such as

- 1) J Biol Chem (n=2), FEBS J (n=2); FASEB J (n=1), Sci Report (n=2), Int J Mol Sci (n=3); Biochemical Pharmacol (n=2), J Med Chem (n=2), Eur J Med Chem (n=2); Front Immunol (n=1);
- 2) N Eng J Med (n=1) as a co-author, Eur Resp J (n=8), Thorax (n=1), Am. J. Physiol. Lung Cell Mol Physiol (n=2), J. Virol (n=1).

The significance and impact of Team 2 research are also exemplified by the number of citations from original articles published in the period from 2016 to 2021. Common papers between different teams in the unit point towards combining available resources and synergies.

Team 2 is now actively involved in the EU collaborative research COST action (acronym: ProteoCure) dealing with targeting proteolysis and proteome remodelling. This collaborative platform allows international postdocs and know-how exchange. In addition, they are also involved in a public-private international cathepsin C consortium (acronym: ICat-CC). The International Cathepsin-C Consortium (ICat-CC) was set up in 2016 as collaboration effort of world's leading specialists from academic labs and industry, working on lysosomal cysteine protease cathepsin C. As a result, the 3rd International Symposium on Cathepsin C, IsyCatC III was organised in Tours/France in April 2022.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	3
Lecturer and associate lecturer	4
Senior scientist (Directeur de recherche, DR) and associate	0
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)	3
Subtotal permanent personnel in active employment	11
Non-permanent teacher researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	2
Subtotal non-permanent personnel	3
Total	14

EVALUATION

Overall assessment of the team

The overall performance of the team in their research area is outstanding. The members of this team are involved in European and international collaborations/partnership and initiatives in the fields of proteolysis with the objective of understanding pathophysiology and targeting of proteases involved in respiratory diseases. The quality of publications is excellent and their work led to the filing of four patents. The scientific production is in line with the team size and research capacity. Funding as leaders comes from national PHRC (1), Région Centre Val de Loire (10, 5 as PI) and Ligue contre le Cancer régionale (4).

They demonstrated excellent collaborations with 5 industrial partners (INSMED, Hoffmann La Roche, LVMH, Polyphor and GenoScience Pharma) and extensive international collaboration network. The team is involved in organising outstanding International meetings (e.g. Cathepsin Symposium) and dissemination to the public.

Strengths and possibilities linked to the context

The team's projects deal with two major topics:

- 1) Lung proteases and chronic diseases. Here the major goal is to understand the proteolytic mechanisms associated with tissue remodelling in pulmonary diseases
- 2) and targeting of pulmonary proteases.

The major objective is to restore the homeostasis of the proteolytic (protease/antiprotease) balance.

The team is a leader in the field of neutrophilic enzymes such as cathepsins. Their studies conducted together with industrial and academic partners have shown relevance of using cathepsin C as a therapeutic target and opened new perspectives for future therapeutic avenues. Importantly, they have also taken the opportunity of working on respiratory disorders caused by COVID-19. They have analysed neutrophil serine proteases in patients with COVID-19. Their results published in the European Respiratory Journal (Seren et al., 2021) helped to initiate a phase 3 clinical study in patients with COVID-19 (Korkmaz et al., 2020).

The team members established outstanding international collaborations with Comprehensive Pneumology Center, Ludwig-Maximilians-University and Helmholtz Zentrum, Munich, Germany; University of British Columbia, Vancouver, BC, Canada, University of Gdansk, Poland, and Queen's University of Belfast, Belfast, UK.

The Team integrates its research with public-private sectors and advances translational research projects towards the development of therapeutic molecules. Indeed, the team developed different forms of collaborations with private companies such as INSMED, F. Hoffmann-La Roche and Neuprozyme Therapeutics, which led to several common publications. In total the team has published 94 articles (43 as PDC) in high-class international journals (Eur Respir J., FEBS J, and FASEB J) and have also filled four patents. Two of the patents have been conducted with the international cooperation partner University of Gdansk, Poland (Design of selective phosphonates inhibitors for proteinase 3 and diagnosing protocol for Papillon-Lefèvre syndrome by rapid, simple and low-cost analysis of urinary cathepsin C. The team participated in several very important collaborative projects which resulted in outstanding publications in e.g. Am J. Respir Crit Care Med and NEJM. This points outstanding international network in the field of proteases.

The team has also secured outstanding amount of extramural funds of 963 k€. All extramural funds involved either industrial or ANR, PHRC National, Vaincre les Maladie Lysosomales, Labex MablImprove, Projets d'Initiative Académique de Région Centre-Val de Loire...)

They also participate in European network Horizon 2020 PROTEOCURE which gathers 31 countries and 280 PIs giving excellent know-how and technology exchange platform.

The team is engaged in public science activities and disseminating results among actors in the socio-economic world. They have organised symposia (ISyCatC I, II, III) and gave lectures to non-academic partners as well as published articles in magazines for large public. Many members of team2 have activities in research administration, coordinating networks, are members of steering and evaluation committees.

Early career members present their projects in major congresses such as American Society for Pharmacology and Experimental Therapeutics (ASPET), European Respiratory Society (ERS), American Society for Matrix Biology (ASMB) which is an important step in sharing their data with the community but it is also crucial for their career development. For their outstanding work, they have been rewarded with best poster and oral talk prizes.

Weaknesses and risks linked to the context

The team could take higher advantage of exchange programmes to secure better mobility of early career researchers. The cooperative studies might also lead to higher chances of receiving non-commercial grants especially EU grants such as start-up and/or consolidator grants.

RECOMMENDATIONS TO THE TEAM

The translation into the clinics may be very challenging in the medium- and long terms, as targeting proteases may have important side effects for the patients. The team will have to be very cautious in this respect. Due to the high number of lecturers, the team should secure time that will be specifically devoted to research. Although the team becomes extremely successful in translational science, we would recommend not to neglect the basic science.

Team 3: Aerosol therapy and biotherapeutics for respiratory diseases
 Name of the supervisor: Ms Nathalie Heuzé Vourc'h

THEMES OF THE TEAM

The theme of the team is a multidisciplinary and translational research in the field of inhalation therapy. Inhalation therapy refers to drug administration through the airway to the nasal cavity or the lung for systemic or local action. The team activity is constructed on three axes: AXIS 1: preclinical models/methods to study inhalation therapy. AXIS 2: inhaled biotherapeutics. AXIS 3: clinical application of inhalation therapy. This third axis relies on both preclinical studies and clinical studies and is supported by private partnership and institutional ones.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main previous recommendation was 'to get international recognition, not only by producing better publications in high audience journals, but also by making this unique structure known. This could be done by organising more international conferences, which is already the case to some extent, by participating in major conferences and by getting better exposure through communication on social media.'

Team 3 has broadly addressed all the recommendations.

Over the period, the team published 158 manuscripts including 100 original articles (45 as PDC) and 30 review articles (22 as PDC) in basic and clinical core journals with high visibility.

The team has an international visibility with major new collaborations which have also led to significant financial support: EuronanoMed (acronym: INAT), H2020 (acronym: 'FAIR'), VIB grand Challenge program (acronym: 'BCORI').

Team 3 members were invited or selected to present their research results in renowned international meetings: ATS 2016 (San Francisco, USA), ERS 2017 & 2019 (Milan, Italy and Madrid, Spain).

Several members co-organised international conferences even during the pandemic crisis: Therapeutic Monoclonal Antibodies for Respiratory Disease, June 2016; International society of aerosols in medicine congress, 2019; Antibody Industrial Symposium, 2019.

They have tried to increase visibility to the general population via social media, which is more difficult and probably less important.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	5
Lecturer and associate lecturer	0
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	1
Research supporting personnel (PAR)	4
Subtotal permanent personnel in active employment	12
Non-permanent teacher researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	0
PhD Students	5
Subtotal non-permanent personnel	5
Total	17

EVALUATION

Overall assessment of the team

The overall assessment of the unit is outstanding. The team is impressive due to several points: the balance between pharmacists, physicians, physicists, and biologists who all work together respecting their specificity but increasing the efficiency of the team; the broad spectrum of their scientific expertise, from pharmacology to clinical trials via the evaluation of medical devices, but always in the field of inhalator therapy. The level of grants dramatically increased in the last years: three European grants (1 as leader), one PHRC national and two regional, four grants from the Region Centre Val de Loire. Their interaction with both non-academic world and academic partners around the world is impressive. They have numerous collaborations with industrial partners and co-founded Cynbiose Respiratory. The team's production comes from all members and all students are active.

Strengths and possibilities linked to the context

The team has a broad spectrum of action in a specific field, inhalator therapy, has long-standing partnerships with various private industries, has established important academic collaborations, is well supported with high-level grants, seems attractive for students not only in the city of Tours. All the ingredients are there to grow. Their role during the pandemic crisis and changes in respiratory care recognition in general population and public authorities since COVID crisis are unique opportunities.

From 2016 to 2021, the team was organised around three different but complementary axes of inhalation therapy:

These three axes allow them to overcome the whole inhalatory concept. Axes 1 and 2 are really specific of the unit and have supported axis 3 which is the most effective in publishing high-level clinical trials.

Team 3 had a national PHRC as PI was partner in a H2020, and PI of numerous (>10) nonacademic grants.

Over the 2016–2021 period, the team scores 158 publications – including 100 original articles (45 as PDC) and 30 review articles (22 as PDC). The reference journals for the team as PI are: two J. Control. Release, two J. Antimicrob. Chemother, two Br. J. of Pharmacol, all ranking in best speciality journals in pharmacology and pharmacy sciences.

Furthermore, 1 Am. J. Respir. Crit. Care Med., one Lancet Resp. Med., Eur 2. Resp. J, three Ann. Intensive Care, three Crit. Care (n=3), all in the most internationally renowned journals of their discipline in Critical Care Medicine and Respiratory System Journals.

For review articles, the team published in best journal of the speciality, as four Exp. Opin. Drug. Deliv. , two Adv. Drug Deliv. Rev. and two Pharmacol. Ther. Moreover, the team also published in specialised journals in aerosol drug medicine (J. Aerosol Med. Pulm. Drug Deliv. n=8) and biotherapeutics (mAbs n=3) which are closely related to the International Society of Aerosol Medicine and Antibody Society and widely read by these reference communities.

The team is also involved in various European and international collaborations/partnership and initiatives in the fields of respiratory medicine, critical care medicine and inhalation therapy with high-level publications.

The team has filed 8 patent applications filed, 1 is licensed to Nemera and 2 are under maturation programs.

The team is recognised nationally and internationally, as evidenced by its numerous invitations to conferences in the field of aerosol therapy and respiratory medicine, and its participation in both academic and industrial partnerships. For example, the team led a European public-private consortium to develop an inhaled nanomedicine to treat lung fibrosis (Euronanomed III project – INAT, 2018 to 2021) – the project was scaled TRL2 to TRL3.

Weaknesses and risks linked to the context

For the next mandate, the team will continue working on the pharmacology of inhaled pharmaceuticals and be renamed: 'Pharmacology of inhaled pharmaceuticals'. We believe it makes sense to concentrate the team activity on a supportive topic, pharmacotherapy, including inhalation of biotherapeutics. In the other hand, all the part on medical device evaluation is a strong part of the unit, the strategic shift will have to be negotiated cautiously because it will interact within the team and with the teams' partnership.

The difference in availability between researchers and MD-PhDs seems to be a perceived weakness. Notwithstanding, it is a major asset of the team, both in terms of valorisation and the overall orientation of the team project.

RECOMMENDATIONS TO THE TEAM

The team needs to move forward at this stage, we only recommend paying attention to the balances between researchers, students and MD teacher researchers that have made an outstanding team successful in terms of world leadership, publications, valorisation, and recognition.

CONDUCT OF THE INTERVIEWS

Date(s)

Start: 02 février 2023 à 8 h 30

End: 02 février 2023 à 17 h 30

Interview conducted: online

INTERVIEW SCHEDULE

- 8:30 a.m.-8:45 a.m. Presentation of the committee
- 8:45 a.m.-9:25 a.m. Highlights of the Unit by the Director
(20 min presentation, 20 min questions)
- 9:30 a.m.-10 h Team 1: Respiratory infection and immunity (Mustapha Si-Tahar/ Christophe Paget)
(15 min presentation, 15 min questions)
- 10h-10:30 a.m. Team 2: Proteolytic mechanisms in inflammation (Gilles Lalmanach)
(15 min presentation, 15 min questions)
- 10:30 a.m.-11h Team 3: Aerosoltherapy and Biotherapeutics for respiratory diseases (Nathalie Heuzé-Vourc'h)
(15 min presentation, 15 min questions)
- 11h-11:15 a.m. Coffee break
- 11:15 a.m.-12:30 p.m. Closed-door meeting of the committee
- 12:30 p.m.-1:30 p.m. Lunch break
- 1:30 p.m.-14h Meeting with technicians and administrative staff
Spokesperson: Christelle Parent (christelle.parent@univ-tours.fr)
- 14h-2:30 p.m. Meeting with PhDs and postdocs
Spokesperson: Marion Lavergne (marion.lavergne@univ-tours.fr)
- 2:30 p.m.-15 h Meeting with researchers not team leaders
Spokesperson: Antoine Guillon (antoine.guillon@univ-tours.fr)
- 15h-3:15 p.m. Coffee break
- 3:15 p.m.-3:45 p.m. Meeting with the representatives of the local institutions
University of Tours: Catherine Beaumont (catherine.beaumont@univ-tours.fr)
Inserm Delegate: Frédéric Delaleu (frederic.delaleu@inserm.fr), ITMO PMN : Raymond Bazin (raymond.bazin@inserm.fr) et Chantal Boulanger (chantal.boulanger@inserm.fr),
ITMO I3M : Yazdan Yazdanpanah (yazdan.yazdanpanah@inserm.fr) et Evelyne Jouvin-Marche (evelyne.jouvin-marche@inserm.fr), ITMO TS : Franck Lethimonnier (franck.lethimonnier@inserm.fr) et Marie-Josèphe Leroy Zamia (marie-josephe.leroyzamia@inserm.fr)
- 15 h 45-16 h Coffee break
- 16h-4:30 p.m. Closed-door meeting of the committee
- 4:30 p.m.-17h Meeting with the Director (M. Si-Tahar) and Deputy Director (N. Heuzé-Vourc'h)
- 17h-6:30 p.m. Closed-door meeting of the committee

PARTICULAR POINT TO BE MENTIONED

N/A

GENERAL OBSERVATIONS OF THE SUPERVISORS

Hcéres
Département d'évaluation de la recherche

Tours, le 22 juin 2023

Objet : DER-PUR230023011 - CEPR - Centre d'études des pathologies respiratoires.

Au nom de l'unité de recherche CEPR, j'adresse mes sincères remerciements aux membres du comité de visite HCERES pour leur rapport et leurs recommandations.

L'unité de recherche CEPR n'a pas d'observations de portée générale à formuler.

Je vous prie d'agréer l'expression de mes salutations distinguées.

Le Président de l'université de Tours

A. Giacometti

Arnaud GIACOMETTI



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www.hceres.fr

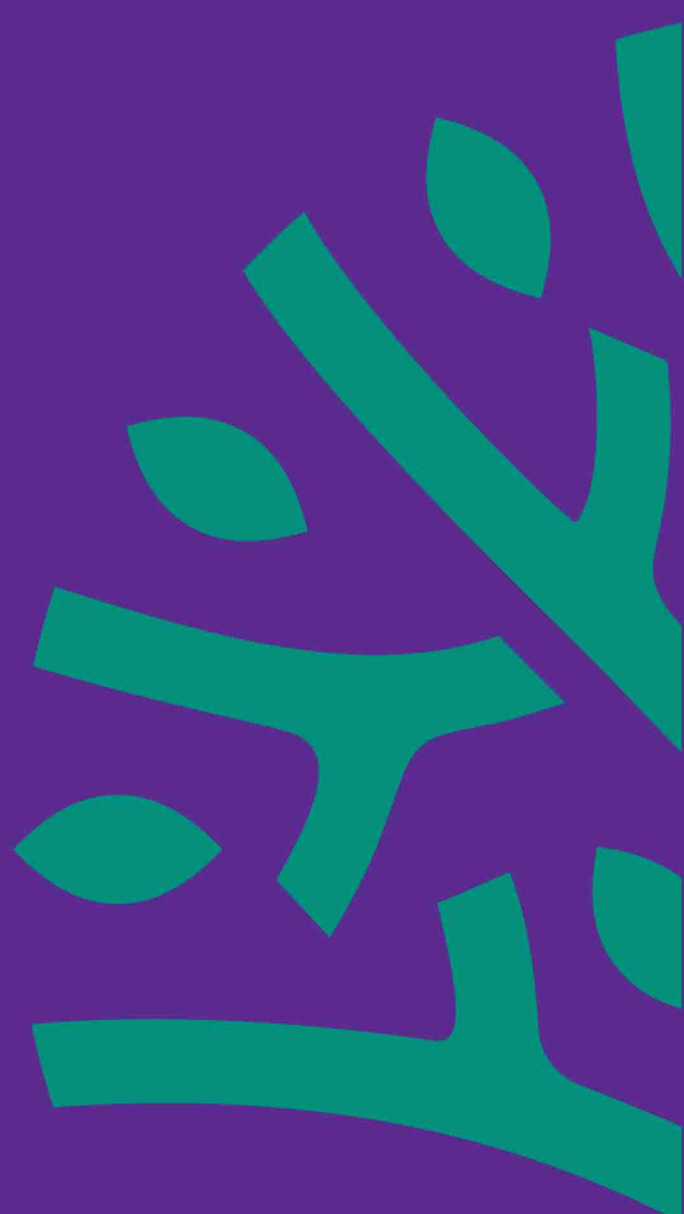
Evaluation of Universities and Schools

Evaluation of research units

Evaluation of the academic formations

Evaluation of the national research organisms

Evaluation and International accreditation



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

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