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(équipe déterminants précoces du développement et de
la santé de l'enfant + épidémiologie des cancers de
l'enfant et de l'adolescent (epicea))**

Rapport Hcéres

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agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of
research units

AERES report on unit:

Epidemiology and biostatistics Sorbonne Paris Cité

Under the supervision of
the following institutions
and research bodies:

Institut National de la Santé Et de la Recherche
Médicale - INSERM

Université Paris Descartes

Institut National d'Études Démographiques - INED



February 2014



agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of
research units

*On behalf of AERES, pursuant to the Decree
of 3 november 2006¹,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the
evaluation of research units department

On behalf of the expert committee,

- Mr Thierry LANG, chair of the
committee

¹ The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).



Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name: Epidemiology and biostatistics Sorbonne Paris Cité

Unit acronym:

Label requested: UMR_S

Present no.: UMR_S 1153

Name of Director
(2013-2014): Mr Philippe RAVAUD

Name of Project Leader
(2015-2019): Mr Philippe RAVAUD

Expert committee members

Chair: Mr Thierry LANG, Université de Toulouse (representative of CNU)

Experts: Ms Isabelle BALDI, Université de Bordeaux

Ms Dominique COSTAGLIOLA, Université Pierre et Marie Curie, Paris
(representative of INSERM)

Mr Scott MONTGOMERY, Örebro University Hospital, University &
Karolinska Institutet, Sweden

Ms Shelia ZAHM, National Cancer Institute, USA

Scientific delegate representing the AERES:

Mr Emmanuel LAGARDE

Representative(s) of the unit's supervising institutions and bodies:

Mr Arnaud DUCRUIX, Université Paris Descartes

Mr Jean-Paul MOATTI, INSERM, ITMO de Santé Publique



1 • Introduction

History and geographical location of the unit

The research center “Epidemiology and biostatistics Sorbonne Paris Cité” has been evaluated by the AERES in 2013. Please refer to the AERES report for unit description. The present report is only related to the evaluation of two teams that used to be part of the INSERM U1018 (CESP) and wish to join the “Epidemiology and biostatistics Sorbonne Paris Cité” in 2015.

AERES nomenclature

SVE1_LS7

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	61	60
N2: Permanent researchers from Institutions and similar positions	26	26
N3: Other permanent staff (without research duties)	31	32
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	14	14
N6: Other contractual staff (without research duties)	67	67
TOTAL N1 to N6	199	199

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	55	
Theses defended	55	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	17	
Qualified research supervisors (with an HDR) or similar positions	60	64



2 • Assessment of the unit

The center has been evaluated by AERES in 2013. The evaluation of the center as a whole was not part of the mission of the visit.



3 • Team-by-team analysis

Team 1 : Early Origin of the child's health and development (ORCHAD)

Name of team leader: Ms Marie-Aline CHARLES

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	
N2: Permanent EPST or EPIC researchers and similar positions	5	6
N3: Other permanent staff (without research duties)	4	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	12	11

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	5



• Detailed assessments

Assessment of scientific quality and outputs

The team has published 106 articles in peer reviewed journals, 38% in the top 10% of the JCR categories. These articles were mainly published in the specialty journals (J Pediatr, Am J Clin Nutr, Epidemiology). Fifty nine invited lectures have been given in national and international meetings. The research is in a valuable area, but in order to have a greater impact the group should attempt to publish more often in journals with a broader readership in terms of scientific discipline. The work on developing cohorts for research is of considerable value and has been very much time-consuming.

Assessment of the unit's academic reputation and appeal

The importance of early exposures is recognised in the aetiology of several important (in terms of public health impact) diseases and thus the focus of this team is within an area of value. This is complemented to a certain extent by a life-course view of subsequent risk accumulation. A strong indication of their reputation and appeal is through their success in attracting additional scientists of notable standing (two senior and two junior researchers). They have a good level of collaboration, but might also consider increasing the amount of international collaboration they participate in. The work on developing cohorts will continue to enhance the team's reputation and appeal to other researchers.

Assessment of the unit's interaction with the social, economic and cultural environment

Some projects have been conducted with industrial partners and results have been used for the French Ministry of Health, as well as a project working with the French Society of Paediatrics to improve nutrition in mothers and infants. Evaluations are conducted by this group and are an important impact activity for academic researchers. Work of note on a national level includes advising on standard growth curves and on breast feeding.

Assessment of the unit's involvement in training through research

They appear to offer a high level of student support for their postgraduate students. Some six doctoral students have completed and five further students are continuing. They participate in teaching but do not run an entire course themselves. They have been involved in the development of a module on a course for Master of Public Health and a course on developmental epidemiology.

Assessment of the strategy and the five-year plan

The increasing use and development of research resources (cohort studies) promise valuable findings through the team's own research and through collaboration. The development of early life measures is of notable interest in France, but also of international relevance. However some of the planned research (for example on specific exposures) would benefit from a broader but also integrated theoretical approach. This should include a broader view of complementary or competing theories of mechanisms. To aid this, a more interdisciplinary or at least multidisciplinary approach (within the team and through collaboration) would be a benefit.

Conclusion

This is a developing group, able to attract new members of staff, that has to balance development of scientific profile and outputs with data collection and raising funds. There is great promise in the area of research and the development of research resources for their own use and collaborators. Publishing for a more general scientific audience would be beneficial, as would add a more interdisciplinary approach to possible biological mechanisms leading to the outcomes of interest.



▪ **Strengths and opportunities:**

This group has the opportunity to use new cohort resources of their own and through collaboration. Through appointments and collaborations they should be sufficiently attractive to attract researchers and collaboration to allow research of a more interdisciplinary nature. This could facilitate the elucidation of biological pathways, including through use of genetic and epigenetic mechanisms, as biological material will be collected.

▪ **Weaknesses and threats:**

So far the group has not had the opportunity to investigate more specific biological pathways that explain the associations that they are examining. There is a danger that associations between early exposures and later disease are explained by an accumulation of unrecorded risks (the associations between low birth weight and raft of socially mediated outcomes for example). The group should ensure that a genuinely life-course approach is indeed adopted to identify causal pathways. Similarly, there is a rather narrow view of some potential mechanisms and a more interdisciplinary approach should be adopted: for example breast feeding may influence child development, not just through nutrition but also through physical contact during breast feeding. Overall, the team members themselves should consider a more expanded and integrated framework for biological processes. The valuable cohort work can be extremely time-consuming, with a tension between raising funds, data collection/planning and scientific output. The value of a cohort can be undermined if there is a loss of continuity in funding, thus adding to the pressure to focus on raising funds.

▪ **Recommendations:**

The group should adopt a more interdisciplinary approach in developing sophisticated and complementary hypotheses for the biological mechanisms involved in mediating disease risk.

The dissemination and scientific strategy should aim to publish more of the team's own work in scientific journals for a more general readership, rather than being limited to more specialised journals.

It will be important to balance carefully activities involving development of resources (and funding) with scientific production.



Team 2 : Epidemiology of childhood and adolescent cancers (EPICEA)

Name of team leader: Ms Jacqueline CLAVEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	3
N3: Other permanent staff (without research duties)	4	8
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	9	9
TOTAL N1 to N6	16	21

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	3



• Detailed assessments

Assessment of scientific quality and outputs

To date, the team scientific output is of importance in the field of the etiology of childhood leukemia, reinforcing the hypothesis of the role of early immune system stimulations, and showing the role of proximity to major roads, gas stations, high-voltage power lines. This has been achieved by the implementation of geographical analysis methods. Another notable finding is the role of the polymorphisms of the genes involved on lymphomatopoiesis. The team also provides the statistics on incidence and survival for all childhood cancer site in France. It seems that some of their observations from these descriptive data could suggest etiological hypothesis. In adults, they also demonstrated the link between lymphoma and light-skin phenotypes (but not with UV radiation exposure), between lymphoid blood disease and occupational exposure to pesticides and with a family history of malignant blood disease.

Between 01/01/2008 and 31/12/2012, the group published 40 articles in peer-reviewed international journals, almost exclusively signed as lead or co-lead author (82% as first or last author). They report 50% of the articles are in the top 20% and 33% in the top 10% of the most cited articles. Two thirds of the articles are in the top 20% of the best journals in the field (defined from the IF rank in the JCR category). The journals in which they have published are mainly high-quality journals for cancer (Cancer Causes and Control, Cancer Epidemiology, Annals of Oncology, International Journal of Cancer, Br J Cancer, Cancer, Eur J Cancer) occupational and environmental health (Occup Environ Med, Environ Health persp, JESEE), and hematology (Blood, Pediatric Blood Cancer, Leukemia).

They have also written books and book chapters and several expert reports.

Assessment of the unit's academic reputation and appeal

Two senior team members are internationally recognized experts in environmental cancer epidemiology and they have been among the first researchers in France to invest in the field of childhood cancer. They are leaders of several international consortium and members of international networks. They are members of several scientific boards in the field of cancer or public health. Evidence of the group's academic reputation and appeal is also provided by the number of students attracted by the team.

Assessment of the unit's interaction with the social, economic and cultural environment

In the field of childhood cancer, their expertise is frequently required by Health authorities. This is demonstrated by their investigation of cancer clusters, which require substantial interaction with the public and patients to explain the results and conclusions. This can be very time-consuming and is an important public health service. They author and contribute to general public books and documentaries on the topic of childhood cancers. Team members participate in working groups of experts from the National Agencies. The team regularly obtains public, association and industrial fundings for their researches.

Assessment of the unit's involvement in training through research

The researchers have contributed greatly to the training of young researchers and to the development of the field through academic teaching (management of a Master in Public Health (DEA of Paris-Sud). The team is involved in training through research and has attributed 40% of their time to this task in the document. They have trained 10 masters students; 6 doctoral students (plus 6 ongoing), 3 medical theses (MD) over the previous period. They are also involved in the supervision of first-cycle courses (DUT, master 1, DIU, pediatric oncology) and in the formation of Public Health residents. All the doctoral students have published their work as first authors.

Assessment of the strategy and the five-year plan

There is no other team in France devoted to childhood cancer and the members of the team have already a recognized and international expertise in the field. There could be important synergies with teams in the new center that deal with pediatric health and related fields.



A major strength of the project is the successful efforts that have been made to build solid and high-quality databases that will help in exploring etiological hypothesis on childhood cancers. These databases are reinforced by the development of the so-called “plateforme” which should add biological and clinical data to the epidemiological collection. The international cooperations that have been built also sound critical, because childhood cancers are not frequent entities and that there is a need for exploring even the less frequent of them.

Concerning the etiological research, the team has fully demonstrated its capacity to analyse risk factors and to generate important discoveries. However, it is not completely clear how they will assess the exposures of interest. Exposure assessment requiring industrial hygiene expertise is needed to characterize jobs whether for the adult’s cancer risk or the offspring’s. Research plans exist for linking geocoded residential histories to environmental exposures. Some external collaborations are listed but it is unclear how they will be able to deal with all the exposures of interest.

The platform for childhood cancer is a new direction in the research program of the team. It not clear how do the members practically intend to switch from etiological epidemiology towards clinical epidemiology. Similarly, the questions that clinicians or researchers have suggested to be priority in the five next years are not clearly stated. Another issue is the coordination of such a large platform. The functioning is not completely described presently.

The team proposes to study all the childhood cancers but their work to date have been focused on leukemia. There are great opportunities to study rare and poorly studied childhood cancers but the way this will be performed is not precisely described.

Conclusion

▪ Strength and opportunities:

- members of the team are internationally well-recognized experts in the field;
- the team has made important and successful efforts in the collection of high quality databases, reinforced by the development of the clinical and biological plateforme;
- the team has great opportunities for important research on poorly studied issues and cancers.

▪ Weaknesses and threats:

- the capacity for supervising young researchers and students appears low;
- the role of a new researcher needs to be clarified since she is a molecular biophysicist but is presented as joining the study of health care pathways;
- the team needs collaboration with experts in the field of environmental and occupational exposures;
- the plans concerning the functioning and scientific strategy of the plateforme are not developed;
- the hypotheses and scientific strategy for studying non-leukemia childhood cancers and adolescent cancers in the next mandate is not presented.

▪ Recommendations:

- on the beginning of the term, there are only two senior researchers in the team (one of whom is applying for an emeritus position). For this reason, there is a need for strenghtening the team with additional researchers, as mentioned, some of them could be qualified in pediatric oncology. It is not completely clear how the recruitment of the new scientist will reinforce the team. Her training and experience in health physics are valuable, but training in social inequalities was not clear. Another difficulty concerning the composition of the team is the large number of technical staff which will oblige the senior researchers to expend considerable effort finding research support for the staff;
- the team needs collaboration with experts in the field of retrospective assessment of environmental and occupational exposures;
- detailed plans concerning the strategy of the childhood cancer plateforme are needed;
- the hypotheses and scientific strategy for studying non-leukemia childhood cancers and adolescent cancers in the next mandate need to be developed.



4 • Conduct of the visit

Visit date:

Start: February 7, 2014 at 8:30

End: February 7, 2014 at 14:40

Visit site:

Institution: Reid Hall

Address: 4 rue de Chevreuse, Paris

Conduct or programme of visit:

08:30 Welcome to the committee

1. Preliminary meeting of the committee

08:45 Meeting of the committee (closed hearing)

Attending: Committee members, AERES scientific delegate

2. Scientific part

9:00 Presentation of AERES evaluation and of committee members

(AERES scientific delegate Mr Emmanuel LAGARDE)

9:10 Presentation of the unit project: Mr Philippe RAVAUD

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

9:30 Scientific Presentation Team 1

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

10:30 Scientific Presentation Team 2

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

3. Meeting with researchers, technicians, doctoral students and post-doctoral fellows

11:30 Three sessions with the committee

Meeting with researchers

Meeting with technicians

Meeting doctoral students and post-doctoral fellows

Attending: Committee members, AERES scientific delegate, without representative of institution, without the direction of the unit and without team leaders



4. Lunch with representatives of Institutions

12:30 Discussion with committee members

Attending: Committee members, AERES scientific delegate, representatives of Université Paris Descartes (Mr Arnaud DUCRUIX), and of INSERM (Ms Christine GUILLARD), without the direction of the unit and without team leaders

5. Meeting with head of unit Mr Philippe RAVAUD

13:20 Session with the committee

6. Close-door meeting of the site visit committee with AERES scientific advisor

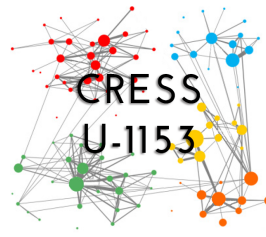
13:40 Deliberation of the committee (closed hearing)

Attending: Committee members, AERES scientific delegate

14:40 End of the site visit



5 • Supervising bodies' general comments



Centre de Recherche Inserm
Epidémiologie et Statistique
Sorbonne Paris Cité – U1153

Rapport AERES S2PUR150007838

CRESS research centre in epidemiology and biostatistics, UMR-S1153, dir. Philippe Ravaud Comments to the AERES committee evaluation report

General Comments

1. Team 1 Early Origin of the Child's health and development team, Marie-Aline Charles

Our team develops a project within the general framework of the developmental origin of adult health and diseases. The evaluation committee acknowledged that this is a valuable research area with potential important impact for public health.

The development of this epidemiological research area in France has needed and still needs long-term investment in birth cohorts setting and coordination. We are glad that the committee has stressed the value of this work. It is indeed time consuming but the investment is worth it for the future research of our team and of many others.

We would like to correct the paragraph on the team involvement in teaching. Indeed, as we have already mentioned one of the team members is a lecturer. He has created de novo and runs from 2012 an entire 24 hr course (50% lectures and 50% tutorials) in epidemiology for students in their 3rd year in the faculty of pharmacy; He is also co-responsible for a course created in 2014 on statistical method in pharmaceutical industry (16h for himself) for students in their 4th year.

Besides, team members have developed in 2012 and run every year a 6hr module in developmental epidemiology as part of a broader program. In addition, two of our doctoral students have been involved in the development of a new MOOC in statistics.

1.1 Interdisciplinary approach

The evaluation committee recommends a more interdisciplinary approach. We totally agree that interdisciplinary collaboration is key for success in research in general and particularly in epidemiology.

We probably have not insisted enough on all our collaborations in multiple disciplines other than epidemiology during our oral presentation. These multiple collaborations are listed below by domains with the corresponding institutions

- Sensory science and eating behaviour: INRA-University of Burgundy; Wageningen University
- Cognitive science: Ecole Normale Supérieure
- Neuroscience: Lyon I University
- Psychology: University College London; University of Leeds; Copenhagen University; Nanterre University;
- Sociology of eating behaviour: INRA
- Sociology of education: CNRS-University of Picardie
- Demography: Ined

- Microbiology: Paris Descartes University
 - Epigenetics: Inserm-Paris Descartes University
 - Genetics: MRC-University of Cambridge;
 - Toxicology: Inserm-Paris Descartes University; Anses
 - Nutritional biology: CNRS- Aix-Marseille University
-
- Paediatric endocrinology, MRC-University of Cambridge; University of Barcelona; Inserm-Paris Descartes University
 - General paediatrics: University of Poitiers,
 - Clinical nutrition and physical activity: Pierre et Marie Curie University; Inserm-Lyon University
 - Sleep disorders: Lyon I University, University of Chicago, University of Montreal

1.2 Integrated approach

W/T :The group should ensure that a genuinely life-course approach is indeed adopted to identify causal pathways. Similarly, there is a rather narrow view of some potential mechanisms and a more interdisciplinary approach should be adopted: for example breast feeding may influence child development, not just through nutrition but also through physical contact during breast feeding.

R The group should adopt a more interdisciplinary approach in developing sophisticated and complementary hypotheses for the biological mechanisms involved in mediating disease risk.

We have made the choice to work on the child's health and development with recent data relevant for the French context. Our research output relies on the data from two French cohorts available for analysis. Over the past mandate, we had mainly data covering pregnancy and the first year of life to work on.

Our strategy has been a detailed and one by one analysis of the complex relationships that arise between the maternal and/or infant nutritional status and the later child development always relying on biological plausible relationships.

We feel that this was and still is a necessary step before 1) addressing more deeply biological mechanisms that may underlie the clinical observations 2) building a more integrated view of the importance of early life factors for later health in the 21st century in France, which is obviously our final general objective.

We are well aware that although early life is a very sensitive period to environmental exposures, the pathway to adult chronic diseases relies on a life course accumulation of additive and interactive factors. Our interest has been and will remain for the next mandate a thorough description of the early life factors. However, with the expanding follow-up of our cohorts, we will also be able to develop a "life course approach" integrating early life and later exposures in relation to childhood diseases. The Elfe cohort, which involves around 100 researchers from social sciences, health and environmental teams in a truly multidisciplinary way (<http://www.elfe-france.fr/index.php/en/research/three-main-research-themes>) will allow us to take into account a larger range of factors than what is done in most epidemiological cohorts, although they will be measured directly with less details than in more focused cohorts.

1.3 Biological mechanisms

W/T Overall, So far the group has not had the opportunity to investigate more specific biological pathways that explain the associations that they are examining. There is a danger that associations between early exposures and later disease are explained by an accumulation of unrecorded risks (the associations between low birth weight and raft of socially mediated outcomes for example). The team members themselves should consider a more expanded and integrated framework for biological processes.

The evaluation committee insists on more implication to investigate biological pathways. This is indeed one of our goals for the next mandate, in collaboration with specialised teams in biology. We have already started such collaborations in nutrition, genetics, epigenetics, and toxicology (listed above).

However, it has to be reminded that biological samples increase their value with longer follow-up of cohort participants. This one of the more complex strategic point in cohort management to decide when and for which research question use part of the expendable biological collection. This, in part, explains why we have not developed this approach more largely during the past mandate.

1.4 Balance between activities involving development of resources and scientific production

W/T The valuable cohort work can be extremely time-consuming, with a tension between raising funds, data collection/planning and scientific output. The value of a cohort can be undermined if there is a loss of continuity in funding, thus adding to the pressure to focus on raising funds.

R It will be important to balance carefully activities involving development of resources (and funding) with scientific production.

Certainly, the time devoted to birth cohort coordination has been competing with the time needed for other research tasks. It is one of the contradictions of the French system due to the lack of engineer and technician positions to run the cohort that impose heavy loads on researcher's time. However, coordination of birth cohorts also exposes to a range of different approaches and research questions, which is needed for the development of collaborative multidisciplinary projects. With the recent arrival of new team members and the end of the follow-up of the EDEN cohort in two years time, we feel that we will be able to reach, at the team level, a more balanced situation between the person-time devoted to the development of resources and to the scientific output.

1.5 General readership journals

R The dissemination and scientific strategy should aim to publish more of the team's own work in scientific journals for a more general readership, rather than being limited to more specialised journals.

Publication in journal with a broader readership will be easier in the future when the longer follow-up of the cohorts will allow to concentrate further on childhood diseases or recognised intermediate markers of adult diseases. The team has shown its capability to publish in such journals with a recent publication in the BMJ, and we agree that we should try to submit more articles to such journals in the future.

2. Team 2 EPICEA research team on epidemiology of childhood and adolescent cancer (0755364Y), Jacqueline Clavel

2.1 The team workforce

2.1.1 W/T the capacity for supervising young researchers and students appears low;

R on the beginning of the term, there are only two senior researchers in the team (one of whom is applying for an emeritus position). For this reason, there is a need for strengthening the team with additional researchers, as mentioned, some of them could be qualified in pediatric oncology.

The team has a strong strategy of training students and young researchers: as mentioned by the committee, we have "trained 10 masters students; 6 doctoral students (plus 6 ongoing), 3 medical theses (MD) over the previous period" and "Evidence of the group's academic reputation and appeal is also provided by the number of students attracted by the team"). This strategic activity will be pursued over the next mandate, including by strengthening our capacity for supervision in the future.

The team will start its 2015-2018 mandate with 2 research directors and 1 research associate who has a real background in epidemiology (see below) and a HDR. Besides, the statisticians of the team have got a PhD several years ago under our supervision and are now able to contribute actively to the supervision of students.

In line with the committee, we consider of key importance for our large-scale program (1) to strengthen the team for the future: we have trained 2 young researchers, one of whom is already candidate for a permanent position in Inserm, the other one being currently in postdoc; (2) to strengthen the present potential of the team for research: the works of the new permanent researcher will finally be devoted to etiological research (see § 1.2 below); (3) to strengthen the capacity of the team to contribute to observational clinical research: 1 hospital practitioner specialized in public health and 2 hospital practitioners specialized in pediatric oncology will part-time join the team for the next mandate.

From this point of view, we are convinced that our very strong investment in large innovating and powerful databases, constructed to address various complementary hypotheses and connected with international collaborations, will be very attractive for young scientists, including, PhD students, post-doc fellows and candidate for permanent position in Inserm or University.

2.1.2 *W/T The role of a new researcher needs to be clarified since she is a molecular biophysicist but is presented as joining the study of health care pathways;*

R It is not completely clear how the recruitment of the new scientist will reinforce the team. Her training and experience in health physics are valuable, but training in social inequalities was not clear.

Meanwhile, we had independently reached a similar conclusion after having taken time to discuss the future program of this researcher, and have reoriented it towards research on childhood brain tumors risk factors. This new direction is better suited to her experience and skills. After 12 years of biophysicist activity devoted to anticancer therapy and biological mechanisms of carcinogenesis, she converted to cancer epidemiology and has worked for 7 years on environmental risk factors of cancer and on long-term effect of radiotherapy in childhood cancer long-term survivors. On childhood brain cancers, she will benefit from the 2 large case-control studies we recently finished to collect, with interview data and constitutional DNA.

Besides, the works on care pathways and possible social inequalities will be developed by the hospital practitioners in public health and pediatric oncology, and in collaboration with teams specialized in this field. We will also benefit from exchanges with the EPOPE team, in the CRESS.

2.1.3 *R Another difficulty concerning the composition of the team is the large number of technical staff which will oblige the senior researchers to expend considerable effort finding research support for the staff;*

We are grateful to the committee for its acknowledgement of the considerable effort needed to build large high-quality database and to find the corresponding funds. We have learnt from 2 decades of creation and management of the national registry that such a project deserves this effort, given the richness and diversity of the resulting data and their interest for research. It is crucial to invest in the training and managing of a skilled team, having a solid knowledge of the data, of the quality requirements, of the network organization, of the partners' rules and of the regulatory needs, with the permanent preoccupation of timesaving. Therefore, the members of the team who runs the components of the Platform are to date highly qualified and have gained more and more autonomy. Our financial burden has been softened recently thanks to the attribution of the first permanent Inserm position for the registry. Also, the recurrent support of the registry and our ANR grant Investment for the future provides the funds necessary to the positions, 2 of them being long-term contracts "CDI". We are aware that is a real challenge to conduct such a project with one third of the budget initially submitted, to emerge and stabilize the structure within 10 years, and to manage positions for perennial missions with short-time contracts. However, we know that we are the only French team who could reasonably take the risk of this commitment in this strategic long-term project.

2.2 Collaborations with experts

W/T the team needs collaboration with experts in the field of environmental and occupational exposures;

R the team needs collaboration with experts in the field of retrospective assessment of environmental and occupational exposures;

Actually, we work systematically with experts in the field of environmental and occupational exposures. In addition, we consider it of utmost importance to standardize the assessment of exposures by experts, blindly to case-control status, and to use transparent rules and validated published methods prior to any case-control comparisons. These principles guide us in developing the relevant specific collaborations with experts for each type of environmental exposure under study, and in finding the best available databases (e.g. precise map of the sources of exposures, measurement campaigns, job exposure matrices) and models. We have worked, and still work, with teams specialized in dosimetry, metrology and modeling of exposures to radiation within the IRSN (residential exposures to ionizing radiation due to nuclear plants, and to exposure to radon and telluric gamma radiation); we are working with RTE (company responsible for electricity transport) engineers for individual model-based estimates of residential exposure to ELF-EMF magnetic fields due to proximity to high-voltage power lines, and with experts specialized in the evaluation of atmospheric pollution measurements and modeling within the French Institute for Public Health Surveillance, InVS (Gazel'Air program), AirParif and U1085 (traffic-related benzene exposure and to indicators of air pollution). Similarly, we have started to develop collaborations on environmental exposure to pesticides used for farming, some of them being new, some other prolonging our previous collaborations on occupational exposures. Choosing markers of socioeconomic status, and indicators or health care trajectory relies on the same need of skilled collaborations.

In our works on adult lymphomas (and now in the Interlymph consortium), we have pursued our general strategy of task-standardized case-by-case expert assessment, and we worked with ACTA (agricultural technical coordinating association) and MSA (farmers insurance) experts. We contributed at that time to set up the industrial hygienist team of the InVS health-occupation department and to the 3-year training of one of its first young industrial hygienist on pesticides and solvents exposures. In children, parental occupational exposures are mostly investigated at the international level, because of small numbers, and international expertise contributions for JEM are currently coordinated by the International Agency for research on cancer, IARC. However, our experience in occupational epidemiology was determinant in the construction of our questionnaires on parental occupation (currently for childhood leukemias and brain tumors).

2.3 Strategy for the Platform

*W/T the plans concerning the functioning and scientific strategy of the platform are not developed;
R detailed plans concerning the strategy of the childhood cancer platform are needed;*

The Platform is a developing multidisciplinary nationwide infrastructure, which is driven by the willing of supporting a large range of projects in observational clinical research, translational research and epidemiological research, in line with the objectives of the Investments for the future. Our strategy for during the next mandate is to make the infrastructure able to function and serve high quality research projects. This means to ensure the long term feasibility of standardized data collection complying with high quality criteria, and to set up an adequate governance for data sharing, all this at lowest cost.

After having consolidated the technical bases of the platform and the rules of partnership and data sharing, we will emit calls for expression of interest twice a year, so that teams (including ours) will be able to prepare collaborative projects to access follow-up data and biospecimens stored in the hospital biobanks with standardized annotations from the national registry, and to send questionnaires to the cohort members. The governance has to manage the questions of data sharing and possible conflicts of interest, and to check that a scientific evaluation has been done, and to encourage new external collaborations. Therefore, the bodies of governance include the President of the French society of pediatric oncology, the epidemiologists responsible for the concerned databases and representatives of pediatric oncologists, pathologists, biologists and radiotherapists. The first call should take place next year. A strength of the Platform is that it will make it possible to address serious questions like early toxic effects or long-term side effects of treatments independently from the inclusion in trials and transversally with respect to the types of tumor, it will help to access to tumor material on several criteria even if tumors are spread in several centers over the territory. Our research projects will also directly benefit from the platform through additional questions on individual parental SES or residential history and possibly by better clinical and biological characterizations of the cases. Our objective is that the Platform be ready, with relevant data, quality criteria and adequate governance, when new hypotheses emerge.

2.4 Etiology of solid tumors

W/T the hypotheses and scientific strategy for studying non-leukemia childhood cancers and adolescent cancers in the next mandate is not presented.

R the hypotheses and scientific strategy for studying non-leukemia childhood cancers and adolescent cancers in the next mandate need to be developed

Our strategy for the etiology of solid tumors is very similar to that of leukemias, but our step of research is different. The numbers are smaller, and for some cancers, classifications have very much evolved, pointing topographic, histological, cytological and molecular subtypes with different prognoses, susceptible to reflect as well some etiological heterogeneity.

Therefore we have waited the completion of our latest individual case-control study, which can be pooled to the previous one so that we can work under better conditions of statistical power. Also we needed to have expanded our registry-based national program, which uses geographic information systems to study specific sources of environmental exposures. We have begun to work on childhood brain tumors. Some of our hypotheses concern genetic factors, through family history of cancer, personal history of birth defects, and search of predisposing polymorphisms, perinatal factors, particularly fetal growth and breastfeeding, and environmental exposures, particularly prenatal exposure to pesticides and parental smoking. Since the Committee visit, we have applied with an US and an Australian team for a grant supporting the creation of an international consortium on brain tumors, and with a UK team for support in GWAS funding. On lymphoma and their different subtypes, we have started the analysis of history of early infections. Finally, our works on adolescent are still at a descriptive stage, with the very recent extension of the registration up to the age of 18.

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