I3 - Immunologie-immunopathologie-immunothérapie

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Immunology, Immunopathology, Immunotherapy

I3

Under the supervision of the following institutions and research bodies:

Université Paris 6 - Pierre et Marie Curie

Institut National de la Santé et de la Recherche Médicale

Centre National de la Recherche Scientifique

January 2013

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

Research Units Department

President of AERES

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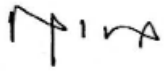
Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the following grades:

- Grading table of the unit: I3: Immunologie-Immunopathologie-Immunothérapie

C1	C2	C3	C4	C5	C6
A	A	A+	C	A	A

- Grading table of the team: ImmunoPhysioPathology

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A	A+

- Grading table of the team: ImmunoTherapy

C1	C2	C3	C4	C5	C6
NN	NN	NN	C	NN	B

- Grading table of the team: Integrative Immunology

C1	C2	C3	C4	C5	C6
B	B	NN	A	A	A

Evaluation report

Unit name:	Immunology, Immunopathology, Immunotherapy
Unit acronym:	I^3
Label requested:	UMR & UMR_S
Present no.:	UMR 7211 & UMR_S 959
Name of Director (2012-2013):	Mr David KLATZMANN
Name of Project Leader (2014-2018):	Mr David KLATZMANN

Expert committee members

Chair:	Ms Florence APPARAILLY, Université Monptellier
Experts:	Mr Jean-Christophe BORIES, Université Paris 7 – Denis Diderot (CoNRS representative)
	Mr Xavier BOSCH, University of Barcelona, Spain
	Mr Irun COHEN, Weizmann Institute, Jerusalem, Israel
	Mr Jan Willen COHEN TERVAERT, Maastricht University, The Netherlands
	Ms Maria Cristina CUTURI, Université de Nantes (INSERM representative)
	Ms Pascale JEANNIN, Université d'Angers (CNU representative)
	Mr Bruno KYEWSKI, German Cancer Research Centre, Heidelberg, Germany
	Mr Joachim L. SCHULTZE, University of Bonn, Germany
	Mr Thierry VANDENDRIESSCHE, Free University Brussels, Belgium

Scientific delegate representing the AERES:

Mr David DOMBROWICZ

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

Mr Yannick JACQUES, CNRS

Ms Chantal LASSERRE, INSERM

Mr Bertrand MEYER, Université Pierre et Marie Curie

1 • Introduction

History and geographical location of the unit

UMR7211/U959 is a mixed research department of the university Pierre et Marie Curie, CNRS and INSERM. It was created in 2009 out of the "Biology and Therapy of Immune Pathologies" unit (BTPI) and it has been directed by Mr David KLATZMANN since then. The unit is currently located in two different buildings on the campus of La Pitié-Salpêtrière university hospital (Paris). UMR7211/U959 is one of the 5 research units of the "Inflammation-Immunopathology-Biotherapy" Hospital-University department (DHU) and member of the "TransImmunom" Laboratory of Excellence (LabEx) programm, both coordinated by Mr David KLATZMANN.

The UMR7211/U959 is named "Immunology-Immunopatholgy-Immunotherapy" (i3) and has consisted of the 4 following teams during the 2009-2012 period, dedicated to the understanding of autoimmune and infectious diseases, as well as cancers:

- **Team 1**: Tolerance – Autoimmunity – Transplantation (TAT) led by B. Salomon, whose aims were to investigate the biology of Treg and designing innovative Tregs-based treatments in autoimmune diseases.
- **Team 2**: Autoreactivity and Alloreactivity to Cancer (A^{2}C) headed by Mr David KLATZMANN, whose global aims was to study autoreactivity and alloreactivity in hematologic cancers, as opposed to fetal-maternal tolerance and autoimmunity.
- **Team 3**: Immunotherapy and Viruses (IV) led by Mr David KLATZMANN, aimed at designing and validating new concepts and practices for efficient immunotherapies in the context of viral diseases.
- **Team 4**: Integrative Immunology: Differentiation, Diversity, Dynamics (I^{2}D^3) co-directed by V. THOMAS-VASSELIN and Mr Adrien SIX, whose aims were to investigate the complexity of the immune system through computerized and mathematical models.

Several scientists with permanent positions, including team 1 leader, will move from January 1st 2014 following the reorganization of the local federative structure (IFR) into the "Centre d'Immunology et des maladies Infectieuses" (CIMI) and i3. The proposed future organisation for the novel i3 unit will be composed of 3 teams, focused on autoimmunity:

Team 1: Immuno-Physiopathology (IP) headed by Mr David KLATZMANN

Team 2: Immuno-Therapy (IT) headed by Mr Bertrand BELLIER

Team 3: Integrative Immunology (I2) headed by Mr Adrien SIX

Management team

Since 2009 the Unit Director has been Mr David KLATZMANN (PU-PHex).

The Unit is organised like a small research pharmaceutical company with a top-bottom and bottom-up research strategy, ranging from fundamental research through to drug development and clinical trials with interactions with clinicians and CIC.

The entire Unit shares 30% of the resources, with the exception of salaries, obtained from grant applications. All teams will benefit from the 2 majors grants (ERC and LabEx) but it is not specified how the money will be split between them.

The proposed organisation appears to be designed to encourage interactions between teams 1, 2 and 3 that are interconnected and fuel each other's work. An executive manager recruited with the LabEx will participate in the i3 management.

AERES nomenclature

SVE1 LS6

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	13 [6.50]	10 [4.50]	8
N2: Permanent researchers from Institutions and similar positions	5 [5.00]	1 [1.00]	1
N3: Other permanent staff (without research duties)	9 [8.50]	6 [6.00]	5
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1 [0.25]	3 [2.05]	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4 [4.00]	6 [5,50]	2
N6: Other contractual staff (without research duties)	3 [3.00]	3 [3.00]	3
TOTAL N1 to N6	**35 [27.25]**	**29 [22.05]**	**20**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	18	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	14	10

2 • Assessment of the unit

Strengths and opportunities

- A very experienced and successful leader with pioneering work, creative and original thinking in the field of immunology.

- Impressive expertise, background and publications related to the basic research topics developped (effect of low-dose IL-2 on Treg, analysis of the antigen-specific repertoire of Treg/eff cells, retro-VLP…).

- Integration of the important evolving field of systems biology with an emphasis on immunology. The integration of the I2 team into the i3 unit is a specific strength as the data processing is often one of the rate-limiting and challenging steps that is known to 'make or break' an 'omics' program. Following the identification of disease- and therapy-associated biomarkers, the i3 unit plans to take advantage of the i2 expertise to ultimately create new opportunities for refining and developing new treatments.

- The connection of cellular immunology and clinical immunology and immunotherapy is an important strategic asset that will keep the Unit focused on its translational goals and will exploit the opportunities to learn from diseases.

- Directed attention to specific topics: The attention of i3 is directed to particular autoimmune conditions (type 1 diabetes..) and emphasizes key immune system elements for translation (natural (n)Treg biology and nTreg-based immunotherapies).

- Impressive expertise and track record of the unit in terms of intellectual property and valorisation including new patents and potentially new spin-off companies based on novel therapeutic strategies to be developed within i3, collaborations with biotechs, translational research with a strong emphasis on immunotherapy.

- Access to important support structures for the planned research (i2B, Transimmunom, CIC-BTi) and close contact with patients and clinical departments. The connection of the i3 Unit with medicine.

- International collaborations: The participation of i3 in international research is an important aspect for its further success.

- Institutional backing and support: The investment of Université Pierre et Marie Curie, Inserm and CNRS in i3 is a critical advantage.

- Numerous technical and administrative staffs (ITA) to support the 3 teams and the director in his management duties, and to run platforms.

Weaknesses and threats

Weaknesses:

- Focus of the systems immunology activities are, on the one hand, very broad (trying to define the whole immune system in one model) and, on the other hand very narrow, (focus on TCR sequences of Treg). A step-wise process might be helpful to achieve milestones and subgoals first.

- Immunotherapy projects plan to explore too many tracks for such a small unit. No priority project has been defined. Though diabetes constitutes one of the main targeted research topics, there is some lack of focus with respect to the broad spectrum of inflammatory/auto-immune diseases being studied. Immunotherapy should rather focus on one disease: diabetes as autoimmune disease but not allergy.

- There is no clear management plan for future recruitment of young and/or more senior scientists.

- The i3 Unit outlines the schedule of formal meetings and presentations designed to foster collaborations, but it does not describe mechanisms to foster informal contacts that so often form the basis for innovative projects and innovative understanding of experimental data.

Threats:

- Only 1 full-time researcher (CR1 Inserm) out of 14 researchers with permanent positions. The other 13 researchers have clinical and/or teatching duties (PU, PU-PH, MCU or MCU-PH) in addition to their research projects.

- Despite the unit's outstanding track record and competitive position, other well-positioned consortia with more manpower could pose a challenge for i3 which faces the typical threats of every research endeavour (competition, too ambitious goals, novel treatments can fail).

- Although the integration of the I2 team (Team 3) into the i3 unit is a strength for 'omics' data processing, it will remain challenging to handle the data stream. There is neither anticipation of the management of the massive informations coming from data collection, nor on the publication leadership in the I2 team that mostly rely on collaborations with other groups for sample patients'collection.

- Lack of clear definition of the patient populations to be targeted among autoimmune diseases as the most likely being able to benefit form the nTreg-based therapies. Similar to small molecule therapy in cancer, where a transition from organ-specific (breast cancer, prostate cancer, colon cancer…) to molecular pathway-specific therapies (targeting the ras, TGFb pathways, Wnt signalling…) seems to take prominence, immunotherapy might also have to evolve towards such an approach. The i3 unit seems to partially understand this by defining the target population as autoimmune disease. This will require a better understanding and development of informative (therapy-associated) biomarkers.

- The major threat that shall be addressed specifically is the assessment of the nTreg repertoire (see recommendations) while there is no true evidence that TCR can influence the functions of nTreg. Nevertheless studying the nTreg repertoire will answer this open question. Thus the project although risky appears very original.

Recommendations

- Integrate and intensify a biomarker program to define those patients within autoimmune diseases who are most likely to benefit from Treg-based therapies.

- Develop a step-wise program with milestones and goals for the integration of the systems immunology program. This will also be a risk minimizing strategy.

- The recruitment and training of personnel and students who suit the aims and projects of the i3 Unit should be better formulated and the unit shall spend more energy for hiring full-time researchers and/or attract young french and foreign fellows (Avenir, ATIP….).

- The existing collaboration with a German team (DKFZ, Heidelberg) team is strongly encouraged and may further strengthen the 'interface' between data collection and high-throughput data processing and analysis.

- The i3 Unit should give attention to engineering opportunities for informal meetings leading to innovative collaborations.

- Put more effort in writing less papers but raising them to higher impact factors.

3 • Detailed assessments

Assessment of scientific quality and outputs

Projects developed in the i3 unit during the last years covered a wide spectrum in the fields of cancer, infections, immunology and immunopathology. Therefore, as expected from such an ambitious project, some published results represented major breakthroughs, while others, in comparison, appeared more modest. However, overall basic and translational research have had a long-standing track-record with several seminal contributions with significant impact in the field of immunology and cancer research. The unit has a truly outstanding scientific record based on the number of scientific publications (319) and the quality of some of these publications in high impact factor general or speciality journals (e.g. J. Clin. Invest., J. Exp. Med, Blood, …) and even general journals with the highest impact factor (e.g. NEJM, Nat Med). About 30% of the papers are in specialized top 5-10% journals with IF>6 (Gut, Arthritis & Rheum, …). The scientific leadership of the unit is excellent with several highly cited papers.

The unit's research also challenged some underlying dogmas in immunology. Both scientific quality and output of the leader of i3 program are very high with very high impact in translating basic science to the clinic. He has been successful in binding research and clinic through the design and validation of novel strategies for true translational immunology. The leader has been extremely successful in securing funding through various competitive grant programs. In particular, major funding was secured to establish a Laboratory of Excellence corresponding to the Transimmunom project. In addition, following a DHU competition, the i2B project was funded. Last but not least, the unit secured a highly competitive grant from the European Research Council (ERC-Advanced Grant), which underscores its genuine outstanding leadership in this field and the high risk/high gain, originality, creativity and feasibility of the planned projects. This provides an objective independent benchmark for scientific excellence.

Finally, the unit also stands out in its efforts towards valorization based on the impressive number of patent applications, licenses and consolidating of start-ups and industrial collaborations. As a whole, the unit has a truly outstanding record on the basis of scientific productivity and quality, fundraising and valorization. The unit took into consideration the recommendation of the previous panel by (i) implementing a stronger focus, (ii) working on fewer projects and (iii) strategize the phenotypic characterization of the Tregs. This was successfully implemented. All 3 teams are composed of highly enthusiastic, creative, intelligent and motivated researchers.

Assessment of the unit's academic reputation and appeal

The leader of i3 has an outstanding academic track record and reputation. The number of publications, patent filings, biotech launched, meetings organized and invitations to prestigious manifestations and leading EU/international events show the dynamics of the unit, as well as the academic reputation of the leader. The list of grants obtained by investigators of i3 is also excellent.

The director of the i3 unit, Mr David KLATZMANN, is involved in international and national projects. Mr David KLATZMANN has a clear role in promoting international projects and contributes to the development of infrastructures of scientific interest. He is currently leading national and international programs.

The i3 research unit has a substantial academic influence that goes beyond the boundaries of the Université Pierre et Marie Curie. The international reputation of the unit is very strong with immunopathology/immune tolerance as the common underlying theme. The team appeals also to young students eager to start a career in science/medicine, consistent with the number of ongoing and already defended PhDs and the number of post-doctoctoral fellows having spent at least a year in the unit. Although attracting several young fellows for PhD and post-doctoral fellowships, the unit however did not yet succeed in recruiting senior researchers from abroad.

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

The unit has gone beyond basic, hypothesis-driven research and has successfully translated their findings into the clinics. Of note, it contributed to major breakthrough innovations in the IL-2-mediated expansion of Treg as a treatment of cryoglobulinemia vasculitis. This may have direct implications beyond cryoglobulinemia vasculitis and may represent a therapeutic approach for other autoimmune diseases (i.e. type 1 diabetes).

The unit is involved in interactions with the social and economic world as it has contributed to 7 patent applications of which 3 are licensed and 2 software programs. It is involved in 3 biotech companies (Epixis, LTK farma and ILTOO Pharma) and 7 clinical trials.

Given the medical relevance of the research it has an intrinsic medico-social impact as the development of the various immune-therapeutics that may arise from the research efforts may ultimately improve patients' quality of life.

Assessment of the unit's organisation and life

There were no significant management issues that were immediately apparent. Due to some recent restructuring, there has been some turnover of more senior scientists. This may create opportunities for the junior principal investigators to consolidate their research efforts. Given the successful fund-raising effort over the past year, it may create an opportunity to recruit a more senior principal investigator (or several junior principal investigators) into the unit.

There is a yearly department council. Together with team leaders and 3 scientists, the director organizes monthly strategic and management meetings (i3 executive board). There is a weekly general journal club, and every other week a journal club specific to each team. Weekly, there are group meetings within each team. An executive manager, funded through i2B and Transimmunom programs, will supervise the organization of i3. The i3 unit also proposes to gather a Scientific Advisory Board (SAB) comprising 3 external experts.

From the proposal and following discussions with different staff members, there seems to be quite an impressive interactive spirit and a tradition of collaborative work. The PhD students and principal investigators did express uninamiously their overall satisfaction. This is clearly reflected by the publication record (the publications with the highest impact factor resulted form internal collaborations), the number of meetings organized, etc.

The proposed organization will provide a close proximity of the unit to clinical department thereby ensuring access to samples from patients as well as immunologic and clinical data to all teams. In addition, the involvement of the unit director in two structuring networks, namely LabEx "Transimmunom" and DHU "i2B", will provide resources and funding to each team.

The unit director is committed to the development of all 3 teams, in particular to team IT (team 2) which could appear weaker than the two other groups though it actively contributes to the activities of the other groups by providing unique immunotherapy-know how, tools and platforms.

The actual structuration of the i3 unit is a bit unusual regarding the team composition as the Director is not only heading the unit and the IP team (team 1) but is also member of the IT team (team 2).

Assessment of the unit's involvement in training through research

The unit has trained 32 PhD students, among which 18 thesis have been defended, and 37 Master students during the last 5 years. This represents a substantial number of PhD students and underscores the strong involvement of the unit in research training. Their PhD research has been (or is being) validated by international peer-reviewed publications.

Each team leader and the unit implement a regular and individualized coaching of doctoral students or trainees. The PhD students are also required to present their data at the lab meeting and are encouraged to do so in scientific meetings. In addition, 6 post-doctoral fellows have spent at least a year in the unit.

No additional commitment into training was mentioned in the "activity and report" and project documents.

PhD students and post-docs are not well-integrated into the scientific activities of the unit, in particular they have no representative at the yearly council of the department.

Assessment of the five-year plan and strategy

The proposed project aims at i) a better characterization of the biology of natural regulatory T cells, ii) improving the understanding of the pathophysiology of autoimmune diseases and iii) to develop biotherapies. The technical approaches, the systems proposed and the close association of basic and clinical research are rather unique. Overall, this is a high-risk/high-gain project (consistent with the ERC criteria that funded this project). However, due to the inclusion of several disease targets and different approaches, it has several build-in contingencies. Not all selected target diseases may respond in a similar impressive manner as the vasculitis study suggested but this would be difficult to predict. Nevertheless, the proposed project is supported by robust data, some of which are published in general journals with the highest impact factors, as well as preliminary data presented during the on-site review (e.g. IT project – asthma model with Retro-VLP). This underscores the feasibility of the proposal. In addition, the construction of the project is coherent, as all teams focus on similar goals and contributed to similar research programs during the previous term. Many groups in France and abroad are studying autoimmune diseases and Treg and as such, the project is not always highly original. Nevertheless, the low dose IL-2 concept to tilt the balance in favour of immune tolerance is truly an orginal "home-grown" concept with broad implications for basic and translational immunology.

Despite these common aims, one potential weakness of the proposal lies in the distinct technological/methodological orientation of team i2, within the unit itself, and its location on the campus.

The project could lead to critical improvement in the treatment of autoimmune diseases and therefore could be of interest for non-academic partners such as biotech or pharmaceutical companies.

The proposed unit has been modified in order to respond to its own scientific evolution (IL-2-based treatment of autoimmune diseases) and to comments of the previous AERES evaluation. The Treg repertoire analysis offers an interesting and original vantage point for these kind of studies. This is further consolidated with external collaborations (e.g. DKFZ, Heidelberg, Germany) and thanks to the recruitment of internal staff members with hands-on experience in this particular field. The use of imaging in Treg analysis offers an additional handle over studying Treg function and trafficking. Though the 'omics' approach seems somewhat more risky and may be more challenging from both the fund-raising and publications perspective, it does provide a unique handle that may result in the discovery of new molecular signatures and hallmarks of normal immune tolerance and abnormal immune homeostasis in pathologic conditions. The proposed approach of combining conventional hypothesis-driven reductionist approach with system biology strategies is an ambitious, "out-of-the-box", yet worthwhile, endeavour that may uncover new underlying biological mechanisms. System biology and 'omics' approaches are already having a major impact on other biomedical disciplines resulting in new and more refined therapies (e.g. oncology) which justifies exploring this further in the context of immunology and immunotherapy. Consolidating possible collaborations with other system biology groups worldwide with a robust track record in the field of immunology, may further strengthen the current I2 effort, in particular.

Overall, there is very reasonable re-focusing on the unit on nTreg-based immunotherapies in the AID (auto-immune diseases) field. In addition, the integration of novel approaches (genomics, sequencing, systems immunology) is very timely and will be necessary to foster this field of basic and translational research. i3 positions itself to have a major impact and leadership position on this particular research field in the life and medical sciences.

4 • Team-by-team analysis

Team 1 : ImmunoPhysioPathology

Name of team leader: Mr David KLATZMANN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	6 [2.84]	6 [2.75]	5
N2: Permanent EPST or EPIC researchers and similar positions	1 [1.00]	0	0
N3: Other permanent staff (without research duties)	1 [1.00]	0	0
N4: Other professors (PREM, ECC, etc.)	0	1 [0.50]	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 [1.00]	4 [3.50]	1
N6: Other contractual staff (without research duties)	1 [1.00]	0	0
TOTAL N1 to N6	**10 [6.84]**	**11 [6.75]**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	9	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	5

Nota: Counts "as at 30/06/2012" corresponds to the current IV I3 team (E3) added with two members of the TAT team and one from A2C team, respectively, that will join iP team for the next term.

• Detailed assessments

Assessment of scientific quality and outputs

The team leader and his team have an outstanding track record in the field of natural Treg biology with an emphasis on translation into clinical practice. Since this field of research is extremely competitive, the achievements and the international reputation are even more impressive. Both scientific quality and output of the team are excellent. The team has published 201 papers in good to very good journals as first and/or senior authors. Several high-impact papers have been published during the last five years in journals ranging from NEJM, JEM, JCI to Science Translational Medicine, clearly stating the focus of the work at i3. In addition, the i3 team has been very successful in filing patents related to their discovery at the same time.

The IP team benefits from its excellent expertise to study the immunopathological mechanisms of chronic inflammatory diseases, to design and validate innovative therapies. They are very successful in bridging research and clinic for true translational immunology.

One of their best and most astonishing success is the discovery that low doses of IL-2 could increase in vivo the number and activity of nTreg in animals models (activity developed by the previous team 1 TAT). The team performed a clinical trial in patients with HCV-induced vasculitis in which they show a decreased number of nTreg (NEJM 2011). The team was the first to show in experimental models and in the clinic that the administration of low doses of IL-2 could restaure nTreg functions in vivo. New clinical trials in other autoimmune diseases are ongoing and a patent has been filed.

Assessment of the team's academic reputation and appeal

As stated above, the leader and his team have an excellent academic reputation. The team is well recognized both nationally and internationally. It has been successful in securing funding through competitive grant applications at the national and international level as coordinateur or as partner. Mainly, the team leader obtained and coordinates an FP7 EU grant DIABIL-2 (2012-2016), a LabEx program (Transimmunom 2012-2020), a DHU, and an ERC grant (TriPod).

The team leader has been invited to speak at 10 international conferences (ISCGT, ASGT, ESGCT 2012, ECCMID 2012, CSHAsia conferences on vaccine design 2012…).

Other team members also participated in international meetings.

The team leader is vice president of the international society for cell and gene therapy of cancer.

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

The team is clearly involved in interactions with the social and economic world as it has contributed to 7 patent applications, is involved in 3 biotech companies (spin-off EPIXIS and ILTOO pharma) and 7 clinical trials. Given the medical relevance of the research it has an intrinsic medico-social impact as the development of the various immunotherapeutics that may arise from the research efforts may ultimately improve the patients' quality of life.

The majority of the team members have significant hospital and teaching duties in addition to their research, thus contributing in many different ways to the the social, economic and cultural environment.

Assessment of the team's organisation and life

No particular problem detected.

Assessment of the team"s involvement in training through research

According to the provided documents this team has a very good track record in student education and also includes the training of MDs in a top research environment. The team has supervised 2 post docs, 3 PhD students and 22 master students.

Members of the team are also involved in different Immunology and Biotherapies courses, they teach, lead and coordinate different master programs.

Assessment of the five-year plan and strategy

The previous 5 year period of i3 was devoted to a rather broad endeavour even including cancer, infection and the development of vaccines; basically covering all major aspects of translational immunology. In this context the outlined plan for the next funding period is much more focused. In fact, the immunopathophysiology team (IP) has two rather broad but interconnected aims:

- To characterize the Treg repertoire during development, aging and diseases.
- To analyze nTreg dynamics in the context of a multidimensional immune balance, under normal and autoimmune conditions.

A central technology for all these aims is NGS (next generation sequencing) of TCRs of nTregs and using this information to follow T cells during homeostasis, disease and therapy. In principle, NGS of TCRs is the most sophisticated and propably the most detailed TCR repertoire analysis that can be performed. There have been several waves of TCR repertoire analyses during the last decades with less sophisticated and less detailed technologies and every time, the scientific community broadly came to the conclusion that no definitive results could be obtained due to insufficient details within the analysis. Whether NGS finally fullfills the requirements to understand whether TCR repertoire analysis will be important for T cell-mediated disease and to optimize T cell-based therapies but will only be seen once the data have been generated and analyzed. In addition, there is no evidence that TCR can influence nTreg functions. This is a very ambitious and innovative projet. The team leader has successful experience in this kind of “multidiciplinary” risky project that involves basic researchers, clinicians and bioinformaticians. The project is also financed by very competitive grants.

The second aim is to compare different parameters in various diseases, before and after treatment, to i) identify signatures and novel candidate drugs, and ii) to better understand the mode of action of biotherapies using in vitro studies. This shall ultimately help clinicians to refine their classification of phenotypically divergent diseases.

Conclusion

● Strengths and opportunities:

- Strong track record in the field of Treg cell analysis and biology in human disease and innovative therapies.

- Continuation of current work.

- Functional Infrastructure for NGS and analysis with corresponding in-house expertise.

- Potential for new patent filings.

- Successful bridging of research and clinic.

● Weaknesses and threats:

Weaknesses

- Even with i2B, ERC and Transimmunom, funding might be on the lower site for such ambitious goals.

Threats

- Other very strong groups and consortia, including industrial partners with larger capacities and funds are also focusing on TCR NGS.

- Other consortia might show that TCR NGS is not as informative as anticipated.

- Other consortia might show that very large numbers of patients are needed to make TCR NGS a useful tool to study nTreg biology as outlined here.

- Lack of experienced, confirmed and full-time senior researchers.

- The nTreg repertoire project assumes that the TCR specificity is important for T cell function (regulatory or effector T cells), this however has not been proven. The project as presented is too general and it is sometimes difficult to understand in which priority order studies will be performed. For example, it was mentioned that the Treg repertoire is going to be analysed in different organs of healthy mouse and human. Will these studies be performed in purified populations, and if so, which ones e. g. induced Treg, natural Treg, CD4+. How will they be defined? During the oral presentation and the poster session, it has been specified that the repertoire analysis will be initiated on nTreg, but many important details remain unclear.

● Recommendations:

- Formulate an alternative strategy in case TCR NGS is not fullfilling its promises and specify at which point will this decision be taken. Consider, in addtion to the TCR repertoire of Tregs, their subset specification according to the organ microenvironment and their target cells (see Campbell and Koch. Nat Rev Immunol. 2011;11:119-30).

- Collaborate within a genomic network (national or international).

- As already outlined by the applicants, pursue active fundraising, including within the industrial sector.

- Recruit and attract full-time researchers.

4 • Team-by-team analysis

Team 2 : ImmunoTherapy

Name of team leader: Mr Bertrand BELLIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	6 [2.84]	2 [0.75]	2
N2: Permanent EPST or EPIC researchers and similar positions	1 [1.00]	0	0
N3: Other permanent staff (without research duties)	1 [1.00]	1 [1.00]	1
N4: Other professors (PREM, ECC, etc.)	0	1 [0.50]	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 [1.00]	1 [1.00]	0
N6: Other contractual staff (without research duties)	1 [1.00]	1 [1.00]	1
TOTAL N1 to N6	**10 [6.84]**	**6 [4.25]**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	9	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	2

Nota: Counts "as at 30/06/2012" corresponds to the current IV I3 team (E3) added with two members of TAT team and one of A2C team, respectively, that will join iP team for the next term.

• Detailed assessments

Assessment of scientific quality and outputs

See corresponding paragraph for team 1

Assessment of theteam's academic reputation and appeal

See corresponding paragraph for team 1

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

See corresponding paragraph for team 1

Assessment of the team's organisation and life

See corresponding paragraph for team 1

Assessment of the team's involvement in training through research

See corresponding paragraph for team 1

Assessment of the five-year plan and strategy

Compared with the previous five-year period, the current plan is much more focused on suppressing imbalanced immunopathology by either inducing or enhancing regulatory T cells or by applying tolerogenic vaccines. This is a very good strategy to focus the research program on, especially in a very competitive research environment, it is scientifically justified and exciting. The program has three major areas of interest, namely i) further development of IL-2-based therapies, ii) engineered nTregs and iii) development of tolerogenic vaccines based on the retro-VLP technology, and applied to targets identified by other team members of the i3 unit. While one might see it as still ambitious, it is a sensible strategy of diversification and a potential platform for future combined immunotherapies, something that can be expected to appear in the near future, similarly to therapy strategies developed in cancer. One could envision to infuse reasonable numbers of ex vivo generated and engineered nTregs followed by boosting with low dose IL-2 therapy with subsequent or intermittent applications of tolerogenic vaccines further tipping the balance from inflammation/autoimmunity towards tolerance. The team seems to be well positioned to bring such strategies towards clinical trials without the difficulties to get different companies, stakeholders and patent holders together first.

The written project is appealing and highly original, even though it lacks precision in the details of the aims. The only limiting point is the feasibility in reaching the envisaged goals with the actual staff of the project proposed by team 2, in other words, do they realistically believe that the team can fully accomplish what they expect for the next 5 years? Team 2 is composed of 6 staff members, including the director, 1AHU, 1 MCU, 2 IE and 1 post-doc.

Conclusion

● Strengths and opportunities:

- Although the new focus on tolerizing immunotherapies for autoimmune disease patients and on complementary approaches is challenging, it is a great opprtunity as well as a logical, timely and original refocus.

- The project is innovative and original with major and expected potential developments.

- Diversification of therapeutic strategies and potential to combine different strategies in future combined immunotherapies.

- It is planned that the IT project will join international networks (i.e. Immune tolerance network). The project of biotherapy will probably be easily supported by grants (INSERM, grants specific for allergic disorders or diabetes).

- The work of the previous team (IV) has led to patents and collaborations with Biotech companies.

● Weaknesses and threats:

- As stated in the SWOT analysis, the current number of staff scientists of the team 2 is not sufficient to develop this ambitious project, though they plan to contract new people through successful grants. None of them is involved full-time in the research project.

- Most full-time scientists have already left or will leave the unit in january 2014.

- As also discussed by the researchers, the current competition in this specific field is a threat in itself.

- It is not clear how the team plans to join international networks to move forward.

- The plan to develop therapy-associated biomarkers needs to be clarified.

- The project priorities are not always well defined and a more specific focus on the key AID (i.e. diabetes) seems justified.

● Recommendations:

- This team might be in the position to interact with patients' advocates and groups to further promote their translational research and open avenues to new funding opportunities, even abroad. This is somewhat alluded to in the 'Grants' section of the submitted documents, but it might be very useful to put sufficient emphasis on securing financial support from important advocating groups outside research.

- Biomarker development program needs to be formulated in more detail. Team 2 should develop a master plan with endpoints and deliverables. To understand the quality of biomarker endpoints, collaboration with biotech focusing on such endpoints would be beneficial. Merely measuring a lot of endpoints might not be sufficient.

- It would be important to restaff team 2 and to motivate scientists to stay for the 5-year project. Failure to do so as well as not restaffing and maintaining principal investigator scientists may profundly impact the chance of success.

4 • Team-by-team analysis

Team 3 : Integrative Immunology

Name of team leader: Mr Adrien SIX

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 [1.17]	2 [1.00]	2
N2: Permanent EPST or EPIC researchers and similar positions	1 [1.00]	1 [0.50]	1
N3: Other permanent staff (without research duties)	1 [1.00]	?	0
N4: Other professors (PREM, ECC, etc.)	1 [0.25]	2 [0.55]	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 [1.00]	2 [1.00]	1
N6: Other contractual staff (without research duties)	2 [2.00]	2 [2.00]	2
TOTAL N1 to N6	**9 [6.42]**	**9 [5.05]**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	3

• Detailed assessments

Assessment of scientific quality and outputs

The integrative immunology team is the youngest part of i3 unit, founded in 2009. During the previous term, team I2D3 has sought to develop bioinformatics tools to integrate immunological, repertoire and transcriptome data. This represents a huge challenge for a young team because the complexity of the systems studied is very demanding and the tools for these do not exist. As a result, although the team has contributed to several projects, it has not yet achieved major breakthroughs and its international outlook appears modest. In line with this, while many reports are submitted or in preparation, most team members are not the main drivers of the papers published in high impact factor journals, though they have made key contributions to these papers. Nevertheless, the i2 team has already contributed significantly to the field of bioinformatics, genomics and systems biology with an emphasis on immunology. The team has developed innovative tools in computer sciences (2 softwares and 2 databases), modelled lymphocyte thymic cell diversity, identified signatures of early vaccine-based therapy efficacy (CompuVac) and biomarkers of autoimmune diseases. The team has published in leading positions in journals with impact factor < 6 (PLoSONE, BMC Bioinformatics, J Infect Dis, Eur J Immunol., Mol Immunol., J Immunol) and coauthored very good to excellent publications in generalist and specialized journals (PLoS Pathog, Arthritis & Rheum, Arthritis Res Therapy, N Engl J Med).

Systems Biology is a very young field and this is even more true for systems immunology. It is therefore not surprising that the approaches used in this research field are very broad and diversified. While some sub-areas have established certain standards many aspects of systems immunology are still under constant development. It is also not yet clear, which different approaches of this young discipline should be integrated and how to integrate them best (e.g. what is the best way for text mining and how can data mining be integrated with automated text mining). Moreover, with increasing data and data structures in the life sciences, the next decade will probably be characterized by continuing diversity of technology development within this field without the appearance of clearly dominating approaches. In light of the early developmental stage the field of systems biology is currently at, team 3 has formulated a rather clear view on how to address important biological aspects of Treg cell biology using systems approaches. This will certainly continue to evolve.

Assessment of the unit's academic reputation and appeal

Although the impression might occur that there are difficulties to attract and keep full-time researchers, this is actually only reflecting the huge demand of individuals with both biological understanding and mathematical and computational expertise.

World-wide there is a shortage of well-trained individuals at the intersection of biology and the mathematical and computational sciences and this is also experienced by i3. Team 3 has however already been very successful in recruiting a group of people with expertise at the interphase of immunology and mathematical and computational sciences. Notably, team 3 attracted a part time researcher who will collaborate on modelling strategies. Additional recruitments are expected.

The i2 team is involved, as a partner team, in two national projects (Transimmunom and DHU I2B) which are coordinated by Mr David KLATZMANN.

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

During the last term, the team reports development of 2 software programs and 2 databases.

Assessment of the unit's organisation and life

Team 3 is composed of 10 staff members, including 3PU, 1 MCU-PH, 1 CR1, 1,5 postdocs, and 3 bioinformatics engineers. Overall, the organization of the team appears coherent. However, it is not clear what added value represents the contribution of an emeritus professor, who is known for his research on parasitology, to a team developing mathematic model of immunology.

The team leader is a member of the unit Executive Board and team meetings are planned to be held in addition to i3 meetings.

Assessment of the unit's involvement in training through research

There seems to be no specific training in computational sciences organized by team 3 except from the teaching duties of team 3 members at Université Pierre et Marie Curie. The team leader is a professor of immunology at Université Pierre et Marie Curie and heads the immunology specialty. He coordinates several Master in Sc immunology curricula. He also develops international programs with Mahidol University Thailand, "Medical Biotechnologies & Biotherapies", and India "Systems immunology and genetics of infectious diseases". Another team member is teaching in the M2 "Biology of aging" Paris 5, Paris 7.

It is not clear how team 3 will recruit young scientists.

Assessment of the five-year plan and strategy

The i2 team lays out a very broad and ambitious program with many aspects of immunology to be covered and at the same time also covering many aspects of technology development in many areas (algorithms, tools, databases, IT infrastructures). On this basis three specific project areas are formulated:

- ImmunoComplexiT : statistical and computer modelling of T-cell lymphocyte differentiation dynamics.

- Cross-phenotyping & biomarker discovery in inflammatory/autoimmune diseases, applying the statistical analysis schemes to the clinical and biological data related to the AID diseases studied by other i3 teams.

- Modelling of complex immunological data using deep sequencing analyses of TCR repertoire.

Although all these projects are of great interest and very ambitious, the weakness of this proposal lies in the relative technological/methodological isolation of team 3, within the unit and perhaps also beyond. Furthermore, the team will be competing with projects developed at a large scale for example at the NIH (USA). Although the SWOT analysis identified this threat, it may nevertheless jeopardize the feasibility of the program. Considering the size of the team, the area of research to be covered, and the difficulty to secure highly experienced personal, the program might benefit from a prioritization process.

The first project area includes many aspects of T cell biology (lymphocyte differentiation, dynamics at multiscale level, migration, etc. etc.) which are certainly all very interesting, however, it would probably be of great value to prioritize the aspects to be studied first in context of the i3 section areas 1 and 2, develop a plan of small-steps with some define endpoints, milestones and deliverables that would have the greates benefit for section areas 1 and 2 to expedite their work. Along these lines, while the development of graphical modelling languages directly executable by immunologists is certainly of great interest, the development of robust mathematics (as suggested by dynamic computer modelling in collaboration with Microsoft) to describe complex systems is probably more important at this stage.

The second project concerns the use of systems immunology for biomarker discovery. While the application of systems immunology can definitely enhance biomarker discovery, the transition to biomarker development very often limits the usefulness of biomarkers being identified by such approaches. This program would probably benefit greatly by fostering collaborations with biomarker developers (academic or industry) that can guide the discovery process to prioritize efforts in this project.

The third project has two subprojects, the analysis of the NGS TCR data and an unrelated aim to integrate data mining and automated text mining. Again, while the analysis of NGS data clearly should be within the responsibilities of the i2 team, the second subproject requires a more focused approach towards issues studied in sections 1 (immunopathology) and 2 (immunotherapy).

Conclusion

● Strengths and opportunities:

- The integration of the i2 team into i3 itself is an important strength.

- Linking translational research to systems immunology is unique and needs support.

- The i2 team has already shown in a short time frame how to deliver (see publication record).

- Linking systems immunology to therapy development in a focused area and academic environment needs to be tested and i3 seems to be a very good place to do so.

● Weaknesses and threats:

Weaknesses

- Very ambitious and very broad research project plan.

- Lack of focus and prioritization on specific aspects of research program in sections 1 and 2.

Threats

- Recruitment of students and young scientists capable of the broad multi-disciplinary interactions needed to sustain the enterprise. The description and the self-evaluation do not emphasize sufficiently the importance of this issue and how the i3 Unit goes about detecting and dealing with the problem of broadly knowledgeable personnel who are yet expert in their particular fields.

- Funding might not be sufficient.

- Missing connection to larger structures in computational sciences.

- Realization of productive interdisciplinary, collaborative research requires students who are supervised jointly by experts in the diverse fields aiming at collaboration; selected students can serve to bridge the professional gap between the specialized scientists. The program does not elaborate on the need for such students and does not explain the plan for enlisting them into the projects.

The project relies mostly on collaborations for patients' samples and important related issues including management of the massive data collection and publication leadership needs to be considered and anticipated.

● Recommendations:

- Structures such as i3 in general and team 3 in particular require direct access to mathematical and computational sciences. The best way to do so is to incorporate a group of systems immunologists with experience in expertise in both worlds: biology/immunology and mathematics/bioinformatics/computational sciences. The recommendation is to advocate their model wherever they can.

- When integrating systems immunology into a medical/biological research environments, the establishment of strong links to environments purely focusing on mathematical/computational sciences are recommended.

- The i2 team needs to further focus and prioritize their research efforts within i3. Generating added value by combining their expertise with projects of IP and IT teams will be the most successful *modus operandi*..

5 • Conduct of the visit

Visit date:

Start: January 23rd, 2013

End: January 23rd, 2013

Visit site: Hôpital La Pitié-Salpétrière, Paris

Institution: Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, INSERM, CNRS

Address: 83 boulevard de l'Hôpital 75651 Paris Cedex 13

Conduct or programme of visit:

8h30-8h40 Welcome

8h40-8h50 Close meeting of the committee

8h50-9h00 Presentation of committee members and explanation of the rules and procedures for AERES evaluation

9h00-9h50 Presentation of I3 Outcome and Project
(25 minutes of presentation + 25 minutes for questions) *
Mr David KLATZMANN

9h50-10h50 Presentation of the *ImmunoPathology (IP)* project
(30 minutes of presentation + 30 minutes for questions)*
Mr David KLATZMANN

10h50-11h00 Pause

11h00-11h40 Presentation of the *ImmunoTherapy (IT)* project
(20 minutes of presentation + 20 minutes for questions)*
Mr Bertrand BELLIER

11h40-12h30 Presentation of the *Integrative Immunology (I2)* project
(25 minutes of presentation + 25 minutes for questions)*
Mr Adrien SIX

12h30-13h00 Parallel private talks of the committee members with
a. Researchers
b. Students and post-docs
c. Technical staff

13h00-13h15 Meeting of the committee with representatives from institutions: Inserm, CNRS, University

13h15-14h15 Lunch with poster viewing

14h15-17h30 Close meeting of the committee (possibly with the director for the beginning or mid reunion).

17h30 End of the evaluation.

Specific points to be mentioned

Due to late and unexpected events, Mr Xavier BOSCH, Irun COHEN and Joachim SCHULTZE were unable to participate to the on-site visit but provided a written report.

6 • Statistics by field: SVE on 10/06/2013

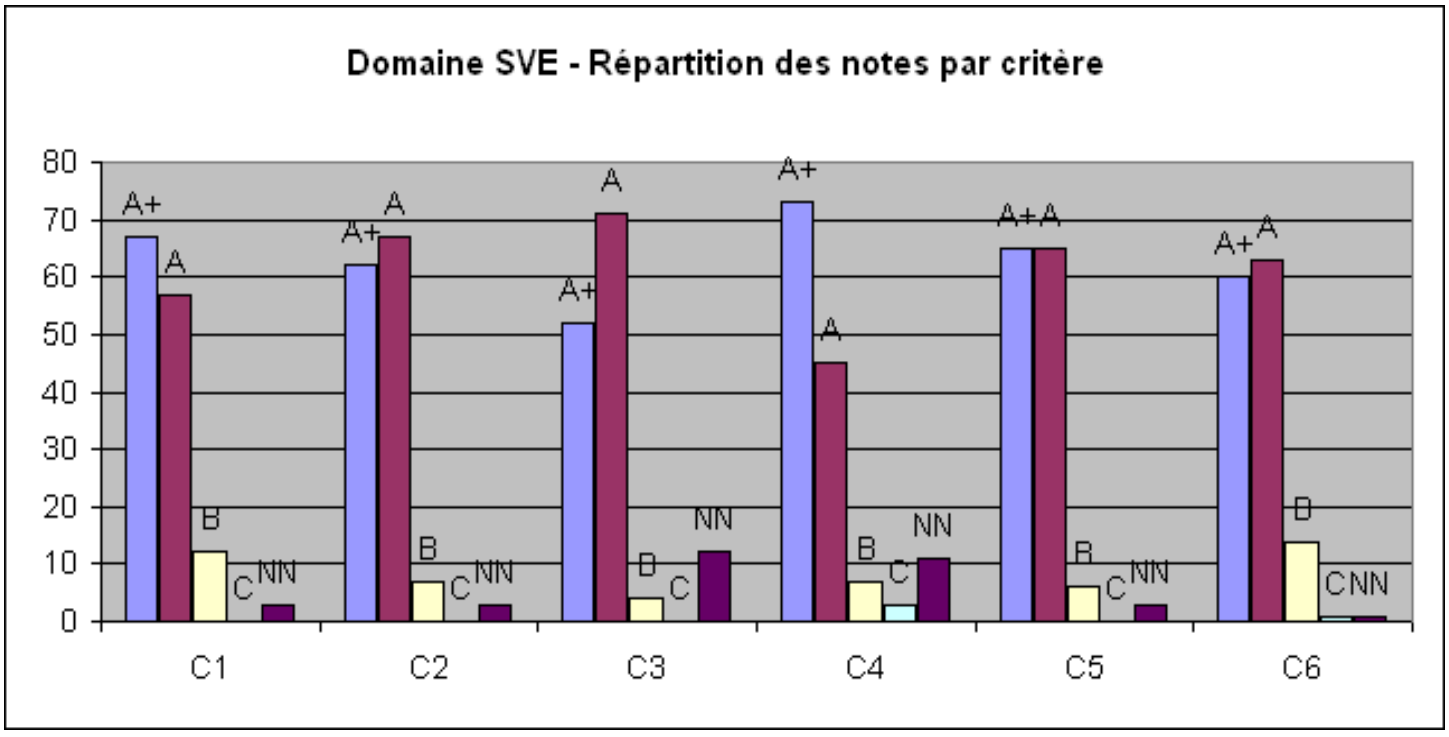
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Paris le 22 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet du Laboratoire Immunologie - Immunopathologie – Immunothérapeutique (I3), porté par M. Klatzamann. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
Tél. 01 44 27 20 09
www.upmc.fr

Assessment of i^3 research unit

We thank the committee for the very positive assessment of the unit.

Regarding *strength and opportunities*, we will just comment on the last one which states "*numerous technical and administrative staff to support the three teams and the director in his management duties and to run platforms*". We would like to mention here that this staff is mostly made of non-permanent personnel paid by the recently obtained grants. As the committee later mentions that, even with these grants, "*funding might be on the lower side for such an ambitious project*" we will appreciate and in fact need more support from our institutions for supporting these activities.

Regarding *weaknesses*, we believe that some of those outlined come from the limited size of the documents provided and the limited time allowed for presentations during the visit.

- Regarding our focus on Systems Immunology, specific comments will be found below in the response to the evaluation of the i2 team. We would like just to point to the fact that, as a later mentioned by the committee, we have now acquired recognized competences in the field of systems immunology and have support from a network of collaborators.
- Regarding our focus on analysing the Treg TCR repertoire, we believe this is rather a strength. We expect that this will become a major research area in the near future, and we will be one of the rare research units to have in house both the technologies and the knowledge in systems immunology that are required to translate such results in true discoveries.
- Regarding immunotherapy, we agree that at this stage we should focus on projects suitable with the size of the newly created iT team. Rather than focusing on T1 Diabetes as suggested, for which competition is fierce, we have decided to focus on allergy notably because we have recently started a collaboration with STALLERGENES, the second worldwide company in allergy. Our first results are very encouraging and we will pursue our activities in this field before expanding to other diseases like T1 Diabetes when appropriate.
- Regarding the comments "*plan for future recruitment of young or more seniors scientists*", we would like to stress that we have recently recruited 3 experienced postdocs who are in good position to apply for a permanent scientist position at one of our institutions. Beside, we are still actively looking for at least one established scientist to join the project. As we want to keep the project very focused, we need to recruit a scientist that will re-inforce our structure rather than broaden its scope, a challenging task.

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Regarding *threat*:

- We would indeed like to recruit additional full time researchers as stated above.
- Regarding the competition and specially the competition with large consortium with more manpower, we have planned to collaborate with some of these consortiums. However, we would like to stress that sometimes small is not only beautiful but efficient! Compared to larger consortium, and because we have the different resources imbedded in our same research unit, we might be more reactive and more capable of adapting to a constantly evolving field.
- Regarding the anticipation of the management of massive information, this has already been anticipated. In fact, we just recruited a researcher who is specialized in database generation and maintenance.
- Concerning the "*lack of clear definition of patients population to be targeted among auto immune diseases*" we are surprised by this comment as, to this exact aim and as mentioned during the presentation, we have designed a clinical trial called "Transreg" where IL-2 will be evaluated in twelve autoimmune diseases such as to better identified those that can benefit from such treatment.
- We also somehow disagree with the comment that we are not focused enough on "*pathways*". The main purpose of our DHU "inflammation-immunopathology-biotherapy" and of our Labex "TransImmunom" is to redefine the nosography of autoimmune diseases based on genetics and pathways, rather than on clinical definitions! We have probably not been clear enough in explaining this to the committee.
- Regarding the "*major threat*" which to the committee is the assessment of the Treg TCR repertoire, we truly don't understand this comment, especially as the committee writes "*there is no true evidence that TCR can influence the function of nTregs*". It is paradigmatic that TCRs influence the function of the T cells as T cell activation is TCR mediated. This is true for effector T cells as it is for natural Tregs. We want also to stress that this specific program is the topic of our ERC grant and this point has not been raised by the reviewers.

Regarding *Recommendations:*

- The first one is already part of our plans;
- The second one is wise and we will implement a step-wise program with milestones and goals for the integration of the systems immunology program;
- The rest of the observations and recommendations make sense and we will try to follow them as much as we can.

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Assessment of the iP team

Again, one the main comment for this team is related to the sequencing of the nTregs TCR. The committee acknowledges that the new technology for TCR sequencing might generate results more informative than those obtained with previous technologies. They again raise the concern that "*there is no evidence that TCR can influence nTreg functions*", that we don't understand. The committee however recognizes that it is a very ambitious and innovative project financed by very competitive grant.

We thank the committee for their list of *strengths and opportunities*.

Regarding our *weaknesses*, we agree that "*our funding might even be on the lower side for our ambitious goals"*. We have already started looking for additional funding. We are already part of an IMI EU application in the field of autoimmune diseases and we plan to raise additional money from the industry.

Regarding *threats*, they are mostly related to the lack of belief by the committee that sequencing of the Tregs' TCRs might be informative. We hope to prove to the committee that they have been too pessimistic in this regard.

Regarding the *recommendations*, we will certainly try to follow the last 3 ones.

Assessment of the iT team

We are pleased that the committee highlighted that the Immunotherapy team's project is "*innovative and highly original with major and expected potential developments"* and the team is "*composed of highly enthusiastic, creative, intelligent and motivated researchers*". We agree "*although the new focus on tolerizing immunotherapies for autoimmune diseases […] is challenging, this is a great opportunity [for us] as well as logical, timely and original refocus*". We also believe that, as mentioned, we are "*well positioned to bring such strategies toward clinical trials*".

We have noted that the committee is concerned about the "*current number of staff scientists of the team [that] is not sufficient to develop this ambitious project*" and thus project priorities should be defined. We are aware of this threat and hope that the project will be highly supported by the different academic institutions (UPMC, CNRS, INSERM). Indeed, this is the only-way to restaff the team for long-term (5-year project) and we agree that failure to do so as well as "*maintaining principal investigator scientists may profoundly impact the chance of success*".

As a result, and as suggested by the committee, we will establish priorities for the starting period of the project and will explore fewer tracks of immunotherapy and focus on one disease. However, considering the very competitive research

environment in diabetes and our opportunities to develop partnership with industries (Stallergenes) and to join international networks (i.e. ITN as international expert), we believe that it is more appropriate to focus first on allergy. The other parts of the project, i.e. diabetes-specific immunotherapies, will be started after new staff recruitments, but will not abandoned. Indeed, diversification of therapeutic strategies and the potential to combine different strategies in future combined immunotherapies have been classified in our *strength*.

Assessment of the i2 team

We acknowledge the committee's evaluation on the past achievements and future project of the i2 team. We are pleased that the proposed working frame model has been understood inasmuch as "*the integration of the i2 team into i3 itself is an important strength*" and "*linking translational research to systems immunology is unique and needs support*". We understand our current weakness that although "*the i2 team has already contributed significantly to the field of bioinformatics, genomics and systems biology [immunology]*", we have brought "*key contributions*" to "*very good to excellent publications*" in which i2 team members were not the apparent "key drivers". We take this point quite seriously, in addition to the discussion that was raised during the evaluation hearing so that "*publication leadership [is] considered and anticipated*". This point is obviously of importance for the correct assessment of the team's contribution.

Concerning the apparent "*lack of focus and prioritization on specific aspects of research program in sections 1 and 2*", we want to clarify that although the overall rationale and strategy of the project advocates the need to consider the immune system as a complex system, therefore taking into account the particular nature of such complex system objects, it does not mean that the entire system must be modeled at once. In fact, modelers like to say that "best models are the simplest". In this line, the i2 team is clearly focusing onto modeling Treg vs. Teff T cell dynamics and TCR repertoire. This work will be carried out in tight collaboration with our computer science collaborators at Microsoft Research, ULB and LIP6/UPMC, with whom we have developed the GOAML modeling platform and who belong to "larger structures in computational sciences". Moreover, automatic text mining is developed under project 3, in collaboration with LIP6/UPMC, to recover specific parameter values from the literature to enrich our computer models of T cell dynamics, in relation to autoimmune disease studies or therapy developments in sections 1 & 2 of the i3 project.

We must also clarify that GOAML is not a mere "*graphical modeling language directly executable by immunologists*" but a robust mathematical and computer modeling platform that alternatively generates differential equation or agent-based simulation code. We believe this shall bring a partial answer to the recommendation of the committee to have "*direct access to mathematical and computational sciences*". In this line, we also anticipate a possible collaboration with theoretical physicist at ENS/UPMC/CNRS. We certainly will continue to "*advocate our model wherever [we] can*" and our ImmunoComplexiT network (RNCS, ISC-PIF) should contribute to this promotion.

We consider the threat regarding that "*funding might not be sufficient*" not relevant, at least for the next term since our laboratory has secured the necessary funding for the current LabEx and ERC projects in which the i2 team is particularly involved. i2 will therefore benefit from these funds. In addition, this involvement clearly aims at "*generating added valued by combining [i2] expertise with projects of IP and IT teams*". In this line, we want to clarify, that the emeritus professor is involved in the theoretical understanding of the network interactions and regulations of the immune system.

Concerning training, i2 has already trained 2 computer scientist post-docs (one recruited by Microsoft Research to sustain our project), 2 PhD and 12 master's students from wet lab immunological data production to dry lab bioinformatics, statistics and mathematical/computer modeling. Our ULB computer scientist collaborator spends 2-3 months per year as UPMC invited professor in i2 team and to teach UPMC students in complex systems and computer sciences with students shared between the two labs. i2 members are involved in teaching Systems Immunology in Master2, under the coordination of i2 leader. We believe this explanation should clarify our true involvement in "*training [students] in computational sciences*" under the supervision of "*experts in the diverse fields*" and that such students "*can serve to bridge the professional gap between the specialized scientists*".

In addition, we have recently recruited two postdocs, one immunologist (specialized in systems immunology and TCR deep sequencing) and one computer scientist (specialized in biomedical database management and data analysis). These recruitments of "*young scientists capable of the broad multi-disciplinary interactions needed to sustain the enterprise*" have been made possible due to the attractiveness of the projects following unsolicited applications. We expect the academic recruitment of these post-docs, in the near future, to sustain the development of i2.

Some of points above have been more thoroughly addressed in the general response and we thank again the committee for its analysis and recommendation that we will carefully take in consideration.