Composantes innées de la réponse immunitaire et différenciation

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

UMR-5164 Composantes innées de la réponse immunitaire et différenciation

From the

Université Bordeaux 2 Victor Segalen

CNRS

Mai 2010

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From the

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CNRS

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: CIRID, Composantes innées de la réponse immunitaire et différenciation

Requested label: UMR CNRS

N° in the case of renewal:

Name of the director: Mr Jean-François MOREAU

Members of the review committee

Committee chairman

Mr Olivier LANTZ, Paris

Other committee members

Mr Dieter KABELITZ, Kiel, Germany

Mr Thomas JACOBS, Hamburg, Germany

Mr Josh BRICKMAN, Edinburgh, UK

Mr Michel PUCÉAT, Evry, France

Ms Marie-Caroline LE BOUSSE-KERDILÈS, Villejuif, France

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

Mr Bruno LUCAS, CoNRS

Mr Pierre GALANAUD, CNU

Observers

AERES scientific advisor

Ms Claude-Agnès REYNAUD

University, School and Research Organization representatives

Mr Alain BLANCHARD, Université Bordeaux 2

Report

1 • Introduction

- Date and execution of the visit

The committee visited the unit on November, 3rd, 2009. After a short introduction by the director the 2 goups presented their past results and their projects. The committee then met the students, the technicians and scientists. The university representative explained how the university will support the unit by providing space and slots. The committee met together to make a global assesment of the unit and prepare a written report.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The UMR-CNRS 5164 belongs to the IFR 66 "Pathologie infectieuse et cancer" (directed by J. Rosenbaum) and is part of The « Ecole Doctorale Sciences de la Vie et de la Santé » of Bordeaux 2 University (directed by R. Marthan). Since its birth in 2003, this research unit has brought together immunologists and stem cell biologists. The unit is localized in University space very close to the hospital with very strong interactions with several hospital department: clinical immunology lab, transplantation unit, nephrology and internal medicine.

- Management team

The unit is directed by JF Moreau who is PU-PH and leads the clinical immunology hospital Lab. He does not head a group. In practice, the unit is managed by the JF Moreau and the 2 group leaders. The hard money is shared by the 2 teams according to their respective sized while the grants are spend by the relevant PI.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	10	13
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9	11
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	6
N7: Number of staff members with a HDR or a similar grade	12	12

2 • Overall appreciation on the research unit

- Summary

The unit is made of 2 teams: one studying ▫▫ T cell biology with connected works on lupus and anti-malaria immunity and the other studying muscle development in xenopus and stem cell biology with emphasis on LIF biology using mouse and human models. The T cell team has developped along the year a unique expertise about ▫▫ T cells with new tools that have and will lead to good publications. The projects are well designed and the interactions between the 3 sub-groups are excellent as demonstrated by the study on ▫▫ T cells in malaria. The strength of this project also stems from the very good links with the clinical activity of some members of the group. This allows the development of relevant clinico-biological questions as examplified by the study on lupus. The second team is more recent and the interactions between the 3 sub-groups are not yet well defined. A solid work has been produced over the last few years. The study of hypoxia and hemoatopoietic cell development is important and needs to focus on hematopoietic stems cells rather than on cell lines. The hiring of a young investigator expert on xenopus development will strengthen this topic if this young investigator is given enough responsibility and autonomy. The head of the team should reinforce links between the existing three 3 sub-groups, by building common themes, which could be on LIF, Tead/Yap or purine biosynthesis. The unit on a whole is well managed with adequate space, facility and good interactions between the groups. The members of the unit carried out all the immunology teaching at Bordeaux.

- General assessment

This unit is the only one studying immunology in Bordeaux. This is both a strength and a threat as the teaching work load is very heavy. The unit is very well managed with a good and nurturing atmosphere for the students and post docs. The space is adequate and the flow cytometry facility is excellent. The connections with the clinical immunology lab are the potential sources of interesting new studies. There are strong interactions between the different members of the unit and good technological and intellectual transfers between the groups. The T cell team has developed an original and interesting expertise with unique tools. There is a good expertise in some aspect of xenopus development. The strategy by the stem cell team is not clear and the strengths/weaknesses of this team compared to the international competition are not well assessed. Both teams are rather small in regards to the aims of their respective projects.

- Recommendations to the head of the research unit

The PIs should consider a larger use of mouse models, as genetic manipulations are a very powerful tool. The PIs should also consider the use of genetic screens to answer some of their questions in an unbiased way when the candidate molecule approach is unsuccessful. The hiring of another PI in the T cell team is important to expand the expertise of the group and allow the team to reach a critical size, high enough to generate still more intellectual and technical interactions. The stem cell team should better define how it envisions its weaknesses, strengths and specific expertise in the context of the international competition. In addition, more responsibility and autonomy should be given to a recently hired new investigator. A journal club at the unit level could be organized

- Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	16
A2: Number of other researchers (recorded in N3) who are active in research	2
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	16/18
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	8

3 • Specific comments on the research unit

- Appreciation on the results

The T cell projects are original and relevant to the physiology of T cells, lupus and malaria. The project of the T cell group is highly original and the recent development of new tools that have already generated interesting new results will certainly lead to high impact papers. Some of the questions addressed by the stem cell group are relevant but the connections between the different projects are not always clear. The number and the quality of the publications is good with journals such as J. Exp. Med, Blood, Cell death and differentiation…. Because of the quality of the equipment and the good relationships set up by the unit director, with the support of the university that has given several technical and teaching positions, the unit has been able to renew the scientists and attract competent investigators. Some investigators are invited to international conferences. The unit has been able to attract a young and successful investigator to strengthen the xenopus sub-group. The investigators are able to upgrade their equipment and to supply 75 % of their supplies and services funding through grants. The different investigators have participated to european networks. The unit is very well managed by the director and the 2 team leaders with good interactions and atmosphere. Being the only immunology unit in Bordeaux the different members have a lot of teaching duties.

- Appreciation on the project

The project for the next four years is feasible and relevant. The recurrent funding is shared while the funding obtained through grant applications is kept separate. This has worked well in the past and should be sufficient for the future. The specific comments for the 2 teams can be found below. It should be noted that the 2 teams study rather different questions and they should prepare to increase in size and/or seek to join other groups in order to enable to split the unit in 2 parts at the end of the 4 year period.

4 • Appreciation team by team and/or project by project

Team 1: Requirements for human T lymphocyte activation in normal and pathological responses

Head: Ms Julie DECHANET-MERVILLE

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	7
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	4
N7: Number of staff members with a HDR or a similar grade	7	6

Team I consists of 3 groups, one studying γδ T-cells, another one studying Malaria and the third one SLE). The common theme of Team I is the analysis of T-lymphocyte activation under physiological and abnormal conditions.

– General remarks:

The presentation of Team I was very well structured and convincing. It was well presented, and it was easily recognized that the three groups do not pursue stand-alone projects on their own but are in fact well connected to each other. It was obvious that the three groups benefit from each other. Overall, the impression of the reviewers was that it is an excellent group of researchers at the forefront of immunological research within their respective field.

– Group 1, Cellular Stress Specificity and Surveillance by γδ T

This group has very successfully studied immune functions of a particular subset of human γδ T-cells characterized by the absence of TCR Vδ2 expression. While the dominant subset of human blood γδ T-cells expressing a TCR composed of Vγ9 and Vδ2 has been well characterized in terms of functional activities and ligand specificity, very little is known about other γδ T-cell subsets. In recent years, this group has demonstrated that a selective expansion of non-Vδ2 γδ T-cells is a characteristic feature of CMV infection. Even more importantly, they have uncovered a very significant cross-reactivity of the T-cell receptors of such γδ T-cells by demonstrating that the non-Vδ2 TCR recognizes shared antigens on CMV-infected target cells and intestinal tumor cells. This observation, published in the high impact factor Journal of Experimental Medicine, paved the way for a systematic search for novel γδ T-cell ligands expressed on infected and transformed cells. They established a monoclonal antibody that recognizes CMV-infected cells as well as certain tumor cells. Together with an external collaborator, they recently identified a peculiar membrane protein as the relevant antigen, and they obtained evidence for a direct involvement of this protein as target antigen for their transduced Vδ5Vγ4 TCR. Interestingly enough, this protein carries homology to MHC-related molecules e.g., CD1, raising the possibility that some γδ T-cells might in fact recognize ligands, possibly lipids, presented by this molecule molecule. These recent results have not yet been published. The argument by the PI that they would like to "finish the story" (i.e., identify ligands bound to this protein) before submitting the data to a high impact leading top journal, is well appreciated.

These results form the basis for the research to be conducted over the next years to come. There are many presently unsolved issues regarding the (patho)physiological role of this protein as a γδ T-cell ligand or presenting molecule, with many implications for immune surveillance in infection and tumor defense. The group has established well functioning collaborations with international groups in areas where they have limited own experience (e.g., structural biology/Mass spectrometry: Dr. Willcox, Birmingham; transgenic mice: Dr. Hayday, London) which will be helpful as the project develops further.

- Publication record 2005-9:

Excellent (JEM 2005, Blood 2008, Cancer Res. 2009, JAMS 2009)

- Leadership and management:

Excellent. The PI is a very experienced researcher; she has successfully raised funds for the group.

- Perspective for next funding period:

Excellent. The publication of their unique results on the presenting molecule will be met by the community with enthusiasm.

- Recommendation:

The group should be funded as requested. In terms of the further development of the project, in addition to the candidate molecule approach, the PI should consider to include unbiased systematic genetic approaches to identify the other distinct membrane molecules that restrict their other □□ T cell clones.

– Group 2, Human Malaria Model:

The group demonstrated that plasmodium-infected erythrocytes or free merozoites are capable to activate V□9V□2 T cells, which are able to kill free merozoites but not infected erythrocytes using a granulysin dependent pathway. This is a very important finding since the effector mechanisms of the immune system against the blood stage of malaria are currently not well understood. They also showed as a proof of concept that □□ T cells are valuable targets for interventions using a primate model of malaria. Very exciting is also their finding on CD16 function on □□ T cells during malaria, which may represent the link between serum levels of malaria specific antibodies and parasitemia in patients.

- Publication record 2005-9:

Very good. The malaria group represents the smallest group but still published in good to very good journals in this highly competitive field (BMC Immunology, JID, Microbes Infect).

- Leadership and management:

Very good. The PI recently moved from the Pasteur Institute to Bordeaux and adjusted their scientific orientation to achieve a maximum of synergistic effects with the scientific approaches within team 1.

- Perspective for next funding period:

Very good. The team was reinforced by a new post-doc. The data (manuscript submitted) on activation and effector mechanisms of □□ T cells against P. falciparum merozoites are very important. Further analysis of the mechanisms of activation will benefit from the methods established in team 1.

- Recommendation:

The group should be funded as requested. The decision to concentrate on the analysis of V□9V□2 T cell function in vitro was right since it allowed a quick start after moving. In terms of the further development of the project the PI should consider to strengthen the analysis of CD16 and antibody mediated effect of V□9V□2 T cells in patients.

– Group 3, Immune Dysfunction in SLE:

This group produced two very original and potentially important findings for the pathophysiology of human SLE, concerning CD8 cells and platelets.

They demonstrated that SLE dendritic cells (DC) activate CD8 T cells through up-regulation of OX40L; this activity can be transferred to normal DCs by incubation with SLE serum. In parallel they observed an increased proportion of activated CD8 cells in the blood of SLE patients. Interestingly, this increase correlated with the lupus activity score. They also showed that the lymphocytes infiltrating the periglomerular region in the kidney of lupus patients are predominantly CD8 cells. These data suggest that, in addition to humoral immunity, cell mediated mechanisms may be operating in a number of SLE lesions. They also show that the activation of CD8 T cells is an indirect consequence of the general dysregulation of alpha interferon and DC.

More recently, they showed that platelets contribute to the hyperexpression of CD40L in SLE patients. Platelets, activated by circulating immune complexes through CD32 may play exert proinflammatory effects. In view of the role of CD40L in humoral immunity the overexpression of this molecule on SLE platelets may have a broader significance in the disease. In fact they confirmed this finding in murine models where they showed that platelet depletion or treatment by clopidogrel improved the parameters of the activity.

These findings led to the proposition of a therapeutic trial of clopidogrel in human SLE.

The project will study the interactions between DC, CD8 T cells and gamma-delta T cells, with a particular emphasis on the role of OX40L. Indeed they have evidence that OX40L plays a role in CD8 T cell activation. They also propose that activated gamma-delta T cells promote alpha interferon secretion by immune complex activated DC.

This program is convincing and original, combining experiments in murine models and the ex vivo study of cells from SLE patients.

In the case of gamma-delta T cells they will obviously benefit from the experience of the other groups of the team.

In conclusion this group develops a very original research in the field of SLE. Starting from observations on the immunological status of SLE patients they uncovered new mechanisms potentially important in this disease. They sought their confirmation in murine models, which will allow them to provide their preclinical validation, and strengthen the feasibility of clinical trials.

- Publication record 2005-9:

Very good regarding the size of the group (Arthritis Rheum 2005, Arthritis Rheum 2007, Intensive Care Medicine 2007). The paper on platelet activation in SLE is under revision.

- Leadership and management:

Excellent. An AHU who worked with the group leader has been recently recruited as Maître de Conferences and will contribute to the increase of the scientific potential. Two MDs who started a PhD thesis with the group leader are now in post doc positions in the United States. They plan to go back to Bordeaux on stable positions in the next few years and will pursue their research in collaboration with or inside the group.

Numerous national and international collaborations have been developed.

- Perspective for next funding period:

Excellent.

Team 2: Pluripotency and early steps of differentiation

Head: Ms Hélène BOEUF

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	5	6

- Results of the past years:

The individuals involved with team 2 have produced solid work over the last few years. This includes a significant amount of micro-array analysis of LIF dependence and the identification of the TEAD transcription factor, that have recently become a focus for early mammalian development as well as on the mechanisms of induction of hematopoietic stem cell quiescence in hypoxia.

- Publication record 2005-9:

Good (JBC 2006, Cell Death and Differentiation 2006, 2008, International J. of Dev Biol 2007, Haematologica 2007, and BMC Genomics 2009, Cell Biology International 2009).

- Leadership and management:

Needs better integration. The PI needs to consider how better to develop the team and focus collaborative efforts.

- Perspective for next funding period:

Concerned. This grouping has made a number of unique discoveries (e.g. TEAD family, role of purine biosynthesis and LIF targets), but needs to find new strategies to capitalize on their past success and do so in a manor that will be competitive internationally.

- Appreciation of the project:

In general, the approaches proposed seem interesting. Also we are concerned that some of the approaches described here might benefit from the use of published reagents that have been tested, rather than the construction of new ones. In general there is a forced fit under the rubric of pluripotency, a precise term that is used somewhat loosely here. Better direct comparative studies could be made that attempted to interface between Xenopus development of specific lineages and mammalian stem cells in those lineages.

Proposals in the area of ES cell self renewal/pluripotency had some interesting aspects, but the committee was concerned that there was little to differentiate the approach taken here from that being developed elsewhere. In the absence of a unique angle, we are concerned that there will be a problem maintaining their competitive edge. The collaborative work with the Xenopus group could be a potential powerful resource, but this needs greater focus. The committee thus strongly recommends the head of the team reinforce links between the existing three 3 sub-groups, by building common themes. These could focus on LIF, Tead/Yap or purine biosynthesis.

The iPS project was ambitious and could benefit from greater thought. We were particularly concerned that as the LIF/STAT3 pathway maintains pluripotency of mouse ES cells by blocking spontaneous differentiation towards extra-embryonic lineages. Consequently, LIF targets might not be sufficient to reprogram human somatic cells. As iPS field of research is highly competitive, the team should first reinforce and expand its capacity to work with human embryonic stem cells to be able to enter this field of research from a better position.

Proposals in the area of Xenopus development are very solid. The TEAD family is becoming a major a focus in recent developmental biology due to the pioneering work of Hiroshi Sasaki and Janet Rossant. The Xenopus group here should be credited with the significant discovery of this family, but they will need to increase their pace in this area to stay competitive. Because of the role of this pathway both in early mammalian development and in Xenopus gastrulation, it could represent an excellent area for the development of interface projects with the ES cell group. One concern is that the entire section of this proposal is based on the work of a previous postdoctoral fellow of Liz Jones' laboratory. We were surprised that this scientist now appointed CR at CNRS is not mentioned anywhere in the proposal, except at the end as a recent hire. However, she was mentioned in the presentation and we would recommend that she be given the status of group leader with a focus on purine biosynthesis.

The proposal derived from the hematopoietic area was sound but raised considerable concern over the over reliance on the FDPC mix cells that is proposed as a model of primitive multipotent progenitors. The track record of this group is solid, especially concerning the mechanisms of the regulation of hematopoietic behaviour by low oxygen concentration, but needs to be focused on primary hematopoietic stem cells rather than on cell lines. We hope that they will be able to use the excellent facilities they have set up to unravel the relationship between Hypoxia and hematopoietic stem cell survival and proliferation. This topic is of importance considering the role of environmental components such as oxygen and ROS level in hematopoietic homeostasis and their potential deregulation in leukemia. To combine hypothermia, hypoxia and hypercapnia for the long-term storage of hematopoietic stem/progenitor cells in view of cell therapy is original and will give a translational dimension to the project. The participation of EFS members to this project will facilitate the bidirectional exchanges between basic research and cell therapy.

The collaboratorative projects lack a certain level of sophistication. Mouse ES cells are LIF dependent and are derived from pre-implantation stages of development. Human ES cells and IPS cells are not strictly LIF dependent and resemble later stages of development more closely. These stages would be more analogous to the Xenopus animal cap. So why is LIF signalling in mouse ES cells comparable to either human IPS generation or Xenopus animal caps? With the limitations mentioned above, the proposal to develop factor free human IPS cells in the absence of any experience working with human ES cells seems very challenging and the committee is concerned about its feasibility. As with some of the ES cell work, it is not clear how this group will be able to position itself relative to the big groups that have been working on human IPS generation for several years now.

- Recommendation:

The group should be funded as requested as they need the opportunity to develop better integration and advance their significant discoveries to another level. The committee acknowledges the originality of the work on LIF and hypoxia and would recommend the team to publish in journals with a focus on stem cell, developmental or cell biology, which would help the group to both raise its profile and bring in further funding. The team should better define how it envisions its weakness, strengths and specific expertise in the context of the international competition. In addition, more responsibility and autonomy should be given to a recently hired new investigator.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Nom de l'équipe : PLURIPOTENCY AND EARLY STEPS OF DIFFERENTIATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Nom de l'équipe : REQUIREMENTS FOR HUMAN T LYMPHOCYTE ACTIVATION IN NORMAL AND PATHOLOGICAL RESPONSES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A+	A

UMR 5164-CNRS
Composantes Innées de la
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Bordeaux, 30 of March 2010

To the AERES committee,

We thank the members of the AERES committee for their evaluation and comments.

Regarding, the evaluation report on **Team 1**, we do not have particular comment to make.

Regarding, the evaluation report on **Team 2**, we would like to correct errors and add precisions which complement some of the comments.

We have noticed several discrepancies between the committee report and the composition of the past and future team as detailed below:

N3: There were 3 post-doc in the past team (*and not 0, as mentioned in the report)*

N4: The number of engineers, technicians and administrative staff with a tenured position will increase from 3 to 5 between past and future (*and not 2 to 4, as mentioned in the report*).

N6: The number of PhD students in the last period of time was 8 (*and not 3, as mentioned in the report*).

Team 2 will include 5 Assistant-Professors or Professors (one is Dean of the Life Sciences Faculty) out of the 7 permanent researchers.

Regarding the team, we want to clarify the concern raised by the committee about a recently appointed scientist (K Massé). This scientist has been hired by the University as Assistant Professor (and not by the CNRS, as mentioned in the report) to work in the *Xenopus* subgroup. She has been given by the UMR, all the opportunities (space, funding and people) to pursue her projects -initiated during her postdoc in UK- in the best conditions. Since her arrival, she has been successfully awarded funding from national charities organisation. Altogether, this will give her complete responsibility to develop her project in a favorable environment.

Besides specific projects developed by the 3 subgroups of team 2, several interface projects have been undertaken at the present time which is not reflected in the report although we agree that we need to focus further on collaborative efforts. Concerning the mES/*Xenopus* interface, we have initiated functional studies in *Xenopus* embryo of genes that have been newly identified in mES cells by extensive microarrays analysis. . We will strengthen those efforts and use the powerful cell lineage analysis of *Xenopus* embryo, in combination with mES cells, to reveal unexpected conserved features in pluripotency and cell differentiation. We will also pursue our efforts to understand the embryonic roles of the murine LIF regulated genes during *Xenopus* development.

The recruitment in 2011 of 6 EFS members in our team justifies a novel interface project devoted to the establishment of "gene-free" iPS cell lines, a still very inefficient and not understood process. Our respective expertises allow us to investigate this challenging and very competitive field. In particular, i) we recently set up a selection procedure of CD34+ cells from leukodepletion filters, a convenient cellular source to derive iPS cells (published in Transfusion, 2010); ii) hypoxia, which favors maintenance and self renewal of HSC is also beneficial for their reprogrammation and iii) we have identified new genes potentially involved in this process.

We hope these complementary informations will be useful,

With best regards,

Pr Jean-François MOREAU
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