Intéraction hôte-greffon-tumeur-ingénierie cellulaire et Tissulaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Host-graft Interactions - Cell and Gene Engineering

From the

Université de Franche Comté

INSERM

EFS

November 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

November 2010

Research Unit

Name of the research unit: Host-graft Interactions - Cell and Gene Engineering

Requested label : UMR_S INSERM, UMR EFS

N° in the case of renewal : UMR 645

Name of the director : M. Philippe SAAS

Members of the review committee

Committee chairman:

M. Olivier LANTZ, Institut Curie, Paris

Other committee members:

Mrs Nathalie CHAPUT, Institut de Cancérologie Gustave Roussy, Villejuif

M. Philippe GRIMBERT, CHU Mondor, Créteil

M. Peter STAEHELI, University of Freiburg, Germany

M. Michael SCHINDLER, Heinrich Pette Institute, Germany

Mrs Annette LARSEN, Hôpital Saint-Antoine, Paris (Inserm CSS7)

M. Moncef GUENOUNOU, UFR Pharmacie, Reims (CNU representative)

Observers

AERES scientific advisor:

Mrs Ana-Maria LENNON

Research Organization representatives

M. Christian DROUET, EFS

Mrs Catherine LABBE JULLIE, CSS INSERM

Report

1 • Introduction

- **Date and execution of the visit:**

The visit took place on November, 5, 2010 from 9 AM to 4 30 PM. After a closed door meeting with the committee members, the former head of the unit presented the main past results. The general strategy of the unit was then described by the new head of the unit. The 2 different group leaders presented their past, present and future projects. A poster session followed. The committee then met with the ITA, students and staff scientists before outlining the main conclusions during a closed door meeting.

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

The unit is the only one in Besançon to be affiliated to INSERM. It is also affiliated to EFS and the University of Franche-Comté. It is located in several buildings (University, hospital and EFS) and uses many EFS and IFR facilities. Most of the permanent researchers have teaching and hospital duties. During the last period, the unit was headed by P TIBERGHIEN and encompassed two research groups : one group studies the mechanisms of and the way to modulate host-graft interaction and the second one studies the rejections of cancers and grafts by the immune system and the way to modulate this process. The first group will be headed by P. SAAS who will be also the head of the unit while the second group will be headed by C. BORG.

- **Management team:**

Philippe SAAS and Christophe BORG are group leaders.

- **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)	16	20
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	19 (15.6 ETP)	17 (13 ETP)
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4 (2.4 ETP)	2 (0.4 ETP)
N6: Number of Ph.D. students (Form 2.7 of the application file)	16	15
N7: Number of staff members with a HDR or a similar grade	17	20

2 • Overall appreciation on the research unit

- **Summary:**

The unit is mainly dedicated to translational research. The publication record is good with abundant production including several papers in the best journals of the categories proposed by the *Journal of Citation Reports* including: "transplantation", "urology and nephrology" or "hematology" (Blood, JASN, Am J Transplantation, Kidney int.) during the last 4 years. The unit has a long standing expertise in cellular therapy with particularly the use of genetically modified effector lymphocyte that was the basis of interesting new results. The interactions between the monitoring unit and the kidney transplant group are highly productive. The expertise of the unit with regards to transplantation epidemiology and teaching is quite unique in France. There is a good integration between the human and the mouse models. The unit was quite attractive as judged by the hiring of new staff scientists, which, however, should not lead to more spreading of the efforts. Indeed, the projects are already quite numerous and more focus would probably be necessary to improve the impact of the published papers.

The students are well mentored and the technical staff is well managed. The technical resources, both internal and external, look appropriate to carry out the proposed work.

- **Strenghts and opportunities:**

Important translational research activity with a nice integration with the 2 Clinical Investigation Centers (CIC): one dedicated to biotherapy and the other to innovative technologies. Good scientific production, good student mentoring. Good working settings.

- **Weaknesses and threats:**

Most of the senior researchers have heavy teaching and hospital work load and there is some lack of focus in the unit. The clinical translation may benefit from a more thorough mechanistic analysis, and would, in some specific cases, also benefit from collaboration with colleagues with expertise in drug development.

- **Recommendations to the head of the research unit:**

Many projects are centered on the specific expertises of the unit and should be continued. Because most of the members of the unit are quite experienced with mixed teaching/hospital appointments the numbers of projects in each team is high. The arrival of new researchers should not lead to an increase of the number of projects but should be the opportunity to acquire the expertise lacking in the unit to allow better mechanistic studies. For the next renewal, the new director of the unit should consider splitting the 2 current big teams into several more focused groups. This would allow a better structuring of the unit and projects. The number of students in the skin engineering platform is rather high for very technical and applied projects.

- **Production results:**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	16
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	4
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years	19
A6: Other relevant item in the field *(i.e. number of first and/or last authors original publications in peer review journals)*	139 out of 266

3 • Specific comments

- **Appreciation on the results:**

The unit is dedicated to translational research with a focus on cellular therapy for malignant diseases or transplantation. The expertise of the unit is original in France. The integration between the different themes seems to be adequate and the different components of the unit are complementary.

The skin engineering platform seems to be productive with regards to the patents applied for.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners:**

New permanent researchers who have been trained in excellent foreign laboratories have been recruited.

Numerous grants have been obtained from public and private sources. There are several collaborations with the industries. Several collaborations are ongoing at the European level. Several patents have been applied for.

- **Appreciation on the strategy, management and life of the research unit:**

The whole unit meets weekly and there are also specific weekly meetings for each team and subgroup. The laboratory council meets every two months. The unit seems to be quite well managed and all the actors seem to be satisfied with the current situation. However, several of the laboratory members who are the most involved in research seem to be principal investigator and lead independent projects. The official recognition of this configuration would enable to better evaluate the necessity, or not, of focusing some groups.

Most of the researchers are heavily involved in teaching with participation in several Master programs at the regional and national level including the management of masters or other teaching modules.

- **Appreciation on the project:**

The specific assessment of the projects will be evaluated for each team.

4 • Appreciation team by team

- **Title of the team and name of the team or project leader :**
- **HOST-GRAFT INTERACTIONS : Philippe SAAS**

TEAM 1: Tolerance et inflammation en transplantation (TIT)

- **Staff members:**

According to the provided document, the delineation between the two teams was not completely clear. In addition, members of the platforms were not clearly included in one or the other of the two teams (TIT or TIMC) and thus could not be evaluated.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	N/A	N/A
N6: Number of Ph.D. students (Form 2.7 of the application file)		6
N7: Number of staff members with a HDR or a similar grade	10	12

- **Appreciation on the results:**

The team 1 (TIT) project is divided into 3 themes:

- Modulation of allo-immunity by IV injection of apoptotic bodies: this topic has been studied for over 10 years and the team has a clear expertise and external visibility on this topic, mainly related to results obtained with in vitro and experimental data.The transfer to humans appears to be very laborious. The current lack of clinical transfer seems to be related to the improvement of the clinical outcome leading to an absence of indication of the procedure.

- Effectors involved in GVHD: important topic and important notoriety of the team in this area. A new direction is being developed on the role of pDCs in the induction of Treg and/or Th17. The project developed on leukaemic pDCs is interesting but is rather divergent from the other topics of the team. However, the cohort of patients is unique. Collaboration with groups specialized in related topics could be considered: other leuckemia of innate cells, biology of pDCs for instance.

- Study of the immune reconstitution after organ transplantation : Recovery of immune system post allograft is a very original topic in France. P SAAS Team has acquired a good notoriety in this field. This topic is mainly developed through translational studies performed on cohorts of renal transplant.

Numerous publications of good quality. However, the number of subjects that are studied likely reduces the ability to publish in high impact journals.

Many national and international collaborations.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:**

This team is attractive because it provides a strong immuno-monitoring platform and good technical support with a large number of technical staff. There is a strong support from the EFS. Several national and international collaborations have been set up. There is a good integration between the university, the hospital and EFS.

Although it appears to be difficult to attract post-doc to Besançon, the team has been able to recruit two senior researchers.

Several grants from public institution and industrial partners.

- **Appreciation on the strategy, management and life of the team:**

Very good contribution and independence of young researchers who independently manage their research and apply for funding. Management is good with well-supervised technicians, regular meetings (weekly bibliographical meetings and data presentation + subgroup meetings). Technical and administrative staff, students and young researchers seemed very satisfied.

Some cutting edge projects, however the proliferation of subjects could lower the level of publication on each topic.

All the researchers have a dual university/hospital appointment. Therefore all the scientists have important teaching involvement including the organisation of masters or other teaching modules.

- **Conclusion :**

Good projects, good scientific production. The focus is translational research and the patient is at the center of the projects even in preclinical ones. An outstanding quality assurance system for a research team due to a strong link with EFS.

Too few full time researchers, too many “small” projects (microvesicles, pDC leukaemia).

The organisation of the group was not clear as the name of the PI for each subject was not clearly provided in the written document (except to some extent in appendix #3). The number of projects for each scientist (especially for those who have teaching and hospital duty) looks too high. Perhaps P SAAS should focus on fewer subjects to be able to publish in journals with higher IF in the future. For the next renewal, the team could be split into several more focused groups. This would allow a better structuring of the team and projects.

- **Title of the team and name of the team or project leader :**
- **HOST-TUMOR INTERACTIONS : Christophe BORG**

TEAM 1: Thérapeutique immuno moléculaire des cancers (TIMC)

- **Staff members:**

There are many academic members not included in the organizational team entitled TIT (P SAAS) or the team entitled TIMC (C. Borg) (cf. Appendix 2). In addition, members of both transfer structures are not clearly included in any one of the two teams (TIT or TIMC).

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1,5	1,5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	N/A	N/A
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	8
N7: Number of staff members with a HDR or a similar grade	5	8

- **Appreciation on the results:**

The project team 2 (TIMC) is divided into 2 themes:

- Signaling pathways that modulate host-tumor-graft interactions (STAT3 and CX3XL1/CX3CR1)

- Development and validation of innovative immunological therapeutics (deltaCD20, NK cells transfer, tumor antigens vaccination)

The projects are original with potential clinical application. However the will to rapidly transfer molecules into the clinic may prevent the analysis of the exact molecular mechanisms involved (particularly STAT3 and CX3CL1 topics) and this may be counter-productive. This has the further effect of decreasing the impact of publications. Two clinical trials using NK cell transfer combined with mabs are innovative and very original in France.

Numerous publications of good quality. However, the number of topics studied likely reduces the ability to publish in high impact journals.

Many national and international collaborations. Many partnerships with industrials (antisoma biotech, invectys biotech, teracetys, Cytheris)

- **Appreciation on the strategy, management and life of the team:**

This team is attractive because it provides a strong immuno-monitoring platform and good technical support with a large number of technical staff. There is a strong support from the EFS. Several national and international collaborations have been set up. There is a good integration between the university, the hospital and EFS.

Although it appears to be difficult to attract post-doc to Besançon, the team has been able to recruit one senior researcher.

Several grants from public institution and industrial partners.

Very good contribution and independence of young researchers who independently manage their research and apply for funding. Management is good with well-supervised technicians, regular meetings (weekly bibliographical meetings and data presentation + subgroups meetings). Technical and administrative staff, students and young researchers seemed very satisfied.

Some cutting edge projects (link between p-STAT3 and MICA expression, CX3CL1 topic). However the lack of a precise description of molecular mechanisms involved could lower the level of publication on each topic.

Contribution of the team members to teaching and to the structuring of the research at the local level.

All but two of the researchers have a dual university/hospital appointment. Therefore all the scientists have important teaching involvement with the organisation of masters.

- **Conclusion :**

Innovative and relevant projects with interesting scientific results and publications. However the molecular mechanisms are not sufficiently explored.

Several cellular clinical trials (2 NK cells transfer along with monoclonal mabs and one adaptive transfer of allogeneic suicide gene modified lymphocytes. C. BORG has a strong expertise in the NK cell field (numerous publications) and P. TIBERGHIEN and C. FERRAND have a strong expertise in allogeneic suicide gene modified lymphocytes with a long experience and numerous publications.

For adoptive transfer of NK cells in patients with colorectal cancer, it seems that inclusion criteria are obsolete. Indeed there is no determination of the mutational status of KRAS and patients with mutated KRAS should not be included in this clinical trial according to international recommendations. An amendment should be proposed. However it should be noted that this team is the only one in France to offer this type of cell therapy treatment. Also, the team has to be praised for this type of initiative as the implementation of this type of approach is very complicated and laborious (financial difficulties, organizational difficulties, cellular production and regulatory difficulties).

Great industrial partnerships, very dynamic translational research program.

Lack of full time researchers but recent recruitment of a young PI.

The young researchers should have been invited to present during the visit since they independently supervise their research and apply for funding.

INTERACTIONS HÔTE-GREFFON-TUMEUR ET INGÉNIERIE CELLULAIRE ET TISSULAIRE	**A**	**A**	**A+**	**A**	**A**
IMMUNOMOLECULAR THERAPIES IN CANCER [SAAS-BORG]	A	A	Non noté	A	A
TOLERANCE AND INFLAMMATION IN TRANSPLANTATION [SAAS-SAAS]	A	A+	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITE DE FRANCHE-COMTE

PRESIDENCE

UNIVERSITÉ DE FRANCHE-COMTÉ

Références à rappeler :
UMR S 645 Hôte-Greffon

Personne chargée du dossier :
Christiane GRILLIER

☎: 03 81 66 58 10

ADRESSE POSTALE :
1, rue Claude Goudimel
25030 Besançon Cedex
Fax : 03 81 66 50 25

BORDEREAU DES PIECES ADRESSEES A :

AERES
Comité d'évaluation de l'UMR Inserm 645

DESIGNATION	OBSERVATIONS
- volet général : observations générales sur le rapport d'évaluation de l'UMR Inserm 645 **- volet corrigeant les erreurs factuelles du rapport d'évaluation**	Pour attribution

Besançon, le 14 mars 2011

Le Président de l'Université,

Pour le Président et par délégation
Le Directeur Général des Services

Claude CONDÉ

Louis BÉRION

Unité Mixte de Recherche U 645
Interaction hôte-greffon et ingénierie cellulaire

Besançon, March 14th, 2011

Prof. Philippe Saas, PhD
UMR645 Inserm / EFS BFC / Université de Franche-Comté
1 Boulevard A Fleming, BP1937
25020 Besançon Cedex

Answer to the report from AERES visiting committee concerning the research unit UMR645: Host-Graft Interactions – Cell and Gene Engineering

We have read in depth the report of the visiting committee. We thank the visiting committee for this report. We were delighted to learn that the committee appreciated: i) the "*important translational research activity with a nice integration with 2 clinical Investigation centers (CIC): one dedicated to biotherapy and the other to innovative technologies"*, ii) our good scientific production ("*The publication record is good with abundant production including several papers in the best journal of the categories proposed by the Journal of Citation Reports: "transplantation", "urology & nephrology" or "hematology" [Blood, JASN, Am J Transplantation, Kidney int. "*]…) and iii) our "*good student mentoring"* and *"good working settings*". We were also pleased to learn that TEAM 1 (Tolérance et Inflammation en Transplantation) has a "*good/important notoriety" or "external visibility*" in the field of "*modulation of allo-immunity by IV apoptotic bodies*", "*Effectors involved in GvHD*" and "*immune reconstitution after organ transplantation*" and that TEAM 2 (Thérapeutique ImmunoMoléculaire des Cancers) is "*the only one in France to offer this type of"* NK "*cell therapy treatment*".

We would like to comment the following remarks of the committee's report.

We fully agree that "*most of the permanent researchers have heavy teaching duties*". However, as mentioned in page 2 of the report, "*the expertise of the unit with regards to transplantation epidemiology and teaching is quite unique in France*" or in page 5 "*Most of the researchers are heavily involved in teaching with participation in several Master programs at the regional and national level including the management of masters or other teaching modules*". Indeed, two members of the unit manage two different M2 master degrees: one dedicated to cell therapy (M2 Ingénierie Cellulaire et Tissulaire) and the other one to transplantation (M2 relation Hôte-Greffon).

Concerning the Staff members and the organizational chart, the report mentions that *"… the delineation between the two teams was not completely clear. Members of the platforms were not clearly included in one of the two teams…*" as well as *"…members of both transfer structures are not*

clearly included in any one of the two teams…". In order to clarify the "who do what" chart, we would like to highlight the following: our research unit includes two research teams ("Tolérance et Inflammation en Transplantation" and "Thérapeutique ImmunoMoléculaire des Cancers") strongly supported by 6 biotechnological platforms as mentioned in the report (please see page 7 and page 8, "... *a strong immuno-monitoring platform and good technical support*"). These 6 platforms are the following: the animal facility, the cell therapy translational research unit, a monoclonal antibody production unit (in collaboration with Diaclone), a skin translational research unit and 2 clinical investigation centers including a immunomonitoring platform involved in patient biological follow-up. These platforms are tightly incorporated in both teams and under the management of unit members. In addition, these platforms include technicians and engineers working under the supervision of the platform manager but who are not included in the organizational chart of the two teams.

We apology for not clearly indicating the name of the respective principal investigators (PI) in the written document as stated in the report page 7: "*…the name of the PI for each subject was not clearly provided in the written document except to some extend in the appendix #3*". However, we provided the name of the PI respectively to their projects during the meeting with the visiting committee. Committee members had time to meet and interact with each of them during the poster session. We would like to provide you with the table below indicating the name of each PI and their research theme.

TEAM 1:	
S Perruche	Modulation of allo-immunity by IV injection of apoptotic bodies
B Gaugler	Effectors (APC, lymphocytes) involved in GVHD
D Ducloux	Immune reconstitution and organ transplantation-related complications
TEAM 2:	
C Borg	Investigating the signaling pathways that modulate host-tumor-graft interactions
C Ferrand / O Adotevi	Development and validation of innovative immunological therapeutic strategies

It was mentioned in the report that the research unit develops too many projects (please see page 4: "*the projects are already quite numerous and more focus would probably be necessary…*"; "*…there is some lack of focus in the unit…*"; "*…the numbers of projects in each team is high…*"). However, as mentioned in the report, most of the projects lead to publications (please see page 6: "*Numerous publications of good quality. However, the number of subjects that are studied likely reduces the ability to publish in high impact journals.*") and these projects are of interest for patient health. Indeed, as mentioned in the report, our research unit is focused on "*translational research*" and "*the Patients is at the center of the projects even in preclinical ones.*". Nevertheless, we will take into account the advice to "*focus on fewer subjects to be able to publish in journals with higher IF in the future. For the next renewal, the team could be split into several more focused groups. This would allow a better structuring of the team and projects.*"

In the project proposed by our research unit, a project developed on leukemic pDC was considered as "*too small*" or "*interesting but is rather divergent from the other topics of the team*". However, as mentioned "*the cohort of patients is unique*". Indeed, a large number (n=46) of leukemic pDC samples have been collected from all over France and collaborations with experts in the field of hematological malignancies or transcriptomic and genomic analysis (including E MacIntyre or C

UMR645 – Etablissement Français du Sang de Bourgogne Franche-Comté – 1 Bd A Fleming BP1937
25020 Besançon CEDEX – France
Tel : +33 (0)3.81.615.615 – Fax : +33 (0)3.81.615.800 – E-Mail : philippe.saas@efs.sante.fr

Preudhomme) have been set up. This leukemic pDC is a valuable model to understand human pDC ontogeny. Furthermore, the study of pDC in the setting of transplantation is common to other TEAM 1 projects.

Concerning the modulation of allo-immune response by intravenous infusion of apoptotic cells, the report mentions that "*The transfer to humans appears to be very laborious*" despite the fact that "*the team have a clear expertise and external visibility on this topic*". This delay in the transfer from the bench to the clinical setting is due to safety and to efficacy considerations and to data obtained in our group. Before a translation to allogeneic hematopoietic cell transplantation setting, we showed that ciclosporin A interferes with the beneficial effects of IV apoptotic cell infusion (Bonnefoy et al., Leukemia, 2008). Ciclosporin A is used in routine alone or in association with mycophenolate mofetil in almost all patients receiving allogeneic hematopoietic cell transplantation. Thus, our cell therapy approach may be ineffective in this setting. An alternative approach to use intravenous apoptotic cell infusion at the time of allogeneic hematopoietic cell transplantation is to avoid ciclosporin A and deplete donor T cells from the graft. We are currently pursuing in this direction and a clinical trial is under preparation.

Then, concerning our adoptive transfer of NK cells in patients with colorectal cancer (NK-EGFR01 study), the experts stated that "*inclusion criteria are obsolete. Indeed there is no determination of the mutational status of KRAS and patients with mutated KRAS should not be included in this clinical trial according to international recommendations. An amendment should be proposed*.". However, it must be stated that in our setting, the antibody directed against EGF-R is not used to target the EGF-R signaling pathway but is used −during a short period of time along with allogeneic NK cell adoptive transfer− to both target cells expressing EGF-R in the hepatic tumors and to trigger cytotoxicity of infused NK cells. These NK cells are infused in the hepatic artery, in the vicinity of the metastasis. Moreover, some industrial monoclonal antibodies (such as RO5083945) optimized for antibody-dependent cytotoxicity are under development. Phase I/II clinical trials (NCT00721266 and EUDRACT #2010-022983-11) were recently approved with similar inclusion criteria and are ongoing.

Lastly, we also regret that "*the young researchers*" have not been "…*invited to present during the visit since they independently supervise their research and apply for funding*". However, in this respect, we followed strictly the request of the AERES committee prior to the visit that only team leaders had to present the projects of the unit.

Yours sincerely

Prof. Philippe SAAS

UMR645 – Etablissement Français du Sang de Bourgogne Franche-Comté – 1 Bd A Fleming BP1937
25020 Besançon CEDEX – France
Tel : +33 (0)3.81.615.615 – Fax : +33 (0)3.81.615.800 – E-Mail : philippe.saas@efs.sante.fr