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

Research Units Department

# AERES report on unit:

## Cell signalling and communication in kidney and prostate cancer

## Under the supervision of the following institutions and research bodies:

University of Strasbourg

INSERM

January 2012

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

*Department Head*

Pierre Glaudes

# Unit

| | |
|---|---|
| Name of unit: | Cell signalling and communication in kidney and prostate cancer |
| Acronym of unit: | |
| Label requested: | UMR_S |
| Present no.: | UMR_S682 |
| Name of Director (2009-2012): | Ms Michèle KEDINGER |
| Name of project leader (2013-2017): | Mr Thierry MASSFELDER |

# Members of the committee of experts

| | |
|---|---|
| Chair: | Ms Palma ROCCHI, Marseille |
| Experts: | Mr Gilles FAVRE, Toulouse |
| | Mr Carlo CATAPANO, Bellinzona, Switzerland |
| | Mr Frédéric JAISSER, Paris (representative of INSERM) |

# Representatives present during the visit

Scientific Delegate representing AERES:

Mr Jean ROSENBAUM

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

Mr Eric WESTHOF (University of Strasbourg)

Mr Gilles BLOCK (INSERM)

# Report

## 1 • Introduction

### Date and conduct of visit:

The site visit took place on January 13th 2011 at Forum de la Faculté de Médecine de Strasbourg. Two months before the visit, each committee member had received a report in English including the description of the work performed in the last four years and the proposed projects for the team directed by Mr Thierry Massfelder. Overall, this report contained all the information required by AERES and enabled an efficient preparation of the visit.

The visit opened by a closed-door session to prepare the review. In a public session, the AERES delegate explained the AERES aims and methodology. Then, the evaluated team presented the project during one hour and fourty five minutes.

After the team presentation the committee was split into three parts to meet students and post-doctoral fellows, engineers and technicians and the researchers with permanent positions.

During lunch time, the committee had a fourty five-minutes closed meeting with representatives from the Université de Strasbourg (including Hôpitaux Universitaires de Strasbourg).

At the end, the committee had 90 minutes closed-door meeting to evaluate the team and prepare the report.

### History and geographical location of the unit, and overall description of its field and activities:

Mr T. Massfelder's team is currently part of INSERM Unit 682. The Inserm Unit 682 directed by Ms Michèle Kedinger was created in January 2007 as a mixed Inserm-Strasbourg University unit. Ms Kedinger will retire at the end of her contract and the 3 teams have chosen to split.

The team of Mr T. Massfelder has now focused on the study of fibrotic and inflammatory components of chronic kidney diseases and renal cell carcinoma.

The proposed research unit that will be directed by Mr T. Massfelder corresponds to the merge of his team that will concentrate on renal cell carcinoma with another team that works on prostate cancer at the Faculty of Medicine (University of Strasbourg, EA4438). The project includes a total of 2 professors and 1 assistant-professor, 1 clinician (PH), 2 researchers, 4 engineers and technicians, 1 post-doc, 4 PhD students and 3 professors, assistant-professors and clinician (associated clinical team) with common priorities to develop an active fundamental, translational and clinical research axis in urologic cancers.

### Management team:

Mr T. Massfelder is proposed as future director of the Inserm Unit.

Unit workforce:

| **Workforce** | **Number** on 06/30/2011 | **Number** on 01/01/2013 | 2013-2017 **Number of producers**** |
|---|---|---|---|
| **N1**: Professors or assistant professors | 5 | 3 | 3 |
| **N2**: EPST or EPIC researchers | 2 | 2 | 2 |
| **N3**: Other professors and researchers | 0 | 3 | 3 |
| **N4**: Engineers, technicians and administrative staff *****on a permanent position | 4 | 4 | |
| **N5**: Engineers, technicians and administrative staff ***** on a non-permanent position | 4 | | |
| **N6**: Postdoctoral students having spent at least 12 months in the unit | 1 | | |
| **N7**: Doctoral students | 4 | | |
| **N8**: PhD defend | 9 | | |
| **N9**: Number of Habilitations to Direct Research (HDR) defended | 0 | | |
| **N10**: People habilitated to direct research or similar | 7 | 6 | |
| **TOTAL N1 to N7** | **20** | **12** | **8** |

***** **If** different, indicate corresponding FTEs in brackets.

****** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.
Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

# 2 • Assessment of the unit

## Overall opinion on the unit:

The overall scientific level, management and facilities are very good in both entities (Inserm U682 and EA4438) that want to merge. The scientific proposal based on the development of an active fundamental translational and clinical research axis in urological cancers is scientifically relevant and coherent. Both groups have in general a very good involvement in national and european networks (ARTP, ESUR). Merging both groups should help increase scientific attractiveness and leadership in the East of France for urological cancer research. This research axis will lean in a proximate future to the Institut Régional du cancer d'Alsace, an integrated facility dedicated to patient care, clinical, translational research and closely linked to fundamental cancer research. The different group leaders want to gather their expertise in urologic field to increase their scientific cooperation, which has been already initiated. In this future project, the team wants to reinforce its basic research programs by developing high level research in the field of activated cell signalling pathways in renal cell carcinoma and prostate cancer that drive treatment resistance.

## Strengths and opportunities:

The project of creation of a new research unit on urological cancers leans on the presence in Strasbourg of two teams working in close collaboration with the Urology unit, the Oncology unit and the laboratory of Pathology of the University Hospital of Strasbourg. The research program of the team benefits from numerous technological platforms (Cancéropôle Grand Est, Strasbourg University, CNRS, Inserm and Mouse Clinical Institute) in Strasbourg.

Innovative approach to identify new pathways involved in renal and prostate cancer treatment resistance.

High level of valorisation and interaction with hospital and private company.

Clear concerns for translational research.

Recently established partnerships with the pharmaceutical industry (IPSEN, Bayer), biotech societies (Urolead, Anda Biologicals), and patents already filed and delivered demonstrate the potential of the team to valorise their scientific results.

## Weaknesses and risks:

The hospitalo-academics constitute an important part of the permanent staff of the team. Furthermore, the future retirement of a CNRS researcher in 2014 will weaken the research potential of the team.

## Recommendations:

The project is highly supported by the committee that however recommends some prioritization for the RCC part, focusing on Lim-1 for example. The use of animal models such as specific transgenic mice will allow addressing more specifically the mechanistic basis of their findings. International collaborations should be also reinforced.

Additional full-time researchers as well as post-doctoral fellows should be hired to reinforce the scientific potential of the team. The committee highly recommends to have both original teams located on the same area in the next future.

# 3 • Detailed assessments

## Assessment of scientific quality and production:

The proposed project is based on elucidating signalling pathways involved in renal cell carcinoma (RCC) and prostate cancer (PC). This project results from the combination of the recognized research expertise of both teams, which previously worked on renal cell carcinoma (Inserm U682) and prostate cancer (EA4438).

The team of Mr Thierry Massfelder has provided in the past original data showing the reactivation of nephrogenic sonic hedgehog (SHH) Gli signalling pathway in human RCC. This risky and original work demonstrated that the reactivation of SHH pathway is crucial for tumor growth, partly through the Akt and NF-kB oncogenic proteins. Using antibody arrays, they found various Gli targets including the developmental transcription factor Lim1. The follow-up of this research topic with clear objectives is highly recommended by the committee.

The other team works on constitutively activated androgen receptor that leads therapeutic resistance in PC. They developed an original yeast-based assay to detect constitutively activated androgen receptor (AR) variant in human samples. By screening different human tumors, they demonstrated the expression of truncated AR variants that lack the ligand-binding domain (LBD) in 83% of metastatic samples. These truncated receptor variants appear to be involved in the castration-resistant progression and represent an interesting target to restore hormone-sensitivity of PC. The following of this project is highly recommended by the committee.

A particular strength of this group is the close collaboration with the Urology, Oncology and Pathology units at the University Hospitals of Strasbourg that allows them to have a good collection of human samples. They took this opportunity to develop unique and original preclinical mouse models of RCC and PC in collaboration with UROLEAD, an innovative spin-off (created and developed by Mr T. Massfelder).

Quality and quantity of publications is in the good range, especially in this competitive field. The group of Mr Massfelder published 6 papers in good impact factor journals like Cancer Research (1), Oncogene (1), Carcinogenesis (3) and Molecular Cancer (1). The other group published 12 original articles also in highly ranked impact factor journals like Cancer Research (1), Endocrinology (2), American Journal of Pathology (1), Human Mutation (2) and International Journal of Cancer (2).

The international position of these groups is difficult to assess but could certainly be better (if jugded on the low number of invitations to international meetings). This is certainly a point that should be improved.

## Assessment of the unit's integration into its environment:

The valorisation part of the projects is very strong with two international patents and the creation of Urolead, a spin off company aimed to provide preclinical models of kidney and prostate cancer with patient tumor xenografts in mice. The company got several awards (Oseo, FEDER, Alsace biovalley and region, Urther) and is well funded. Part of the proposed research in the Unit will benefit of the expertise, tools and financial support from this company. This is also a good way to translate the fundamental research to preclinical/clinical area as well as to industrial partners.

Both groups have a good hability to obtain external financing like InCa (2), ANR emergence and FRM « chimie pour la médecine », LNCC and ARC « subvention libre », which represent a total of 750 000 €. However, the team should reinforce its capacity to obtain more competitive grants.

## Assessment of the research unit's reputation and drawing power:

Few international invitations, but the participation of both groups to the organization of national (ARTP) and European programs (ESUR) is good. The team leader is chairman of the next annual congress of the European Society for Urological Research (ESUR) and the other group leader is permanent vice-president of the ARTP meeting. However, collaboration with foreign laboratories should be reinforced in the future.

Since 2007, they have been able to recruit 2 post-docs, 7 PhD, 9 master 2 students and 14 master 1 students highlighting the good capacity to attract students, especially medical doctors.

However, although two former students are expected to come back from their post-doctoral stage in Belgium and in the US, the team should improve its capacity to attract more foreign post-docs.

## Assessment of the unit's governance and life:

This merging research unit combines the better of two previously independent teams, which refocused their research. No doubt that this will be a beneficial crossfeeding with shared expertise and tools. The proposed director of the team appears to be well appreciated and respected by the members of the team.

## Assessment of the strategy and 5-year project:

The research project is ambitious and innovative which rely on strong data obtained previously in both groups. The international competition on these topics is high but the expertise and hypotheses appeared original and well suited. The research staffs are adequate (4 technicians for 2 full time researchers). Recruitment of a junior researcher as scheduled will be important in the future.

The RCC program on studying the reactivation of SHH-Gli pathway is very risky and original. Only few laboratories are working on these aspects and the follow up of this project focusing on Lim-1 strategy is highly recommended by the committee. However, the program priorities regarding the inhibition of this pathway in tumor growth and invasion should be more ambitious and clarified. Interaction with the local mouse clinical institute should be reinforced in order to develop more ambitious metastatic mice models.

The PC research program based on elucidating the novel functions of the truncated AR receptor variants on gene expression is highly relevant and well structured. The first part of the project is based on elucidating the consequence of the lack of the binding domain of the AR for interaction with its partners using multi-level approach (RMN, crystallography). On the second part, they plan to assess the functions of AR variants on stroma-epithelium communication, invasion, migration and metastatic progression of PC. Lastly, in partnership with different industrial partners (Ipsen, Janssen and Bayer) they are looking for novel compounds that inhibit the interaction of the truncated AR with its regulatory co-factors.

## Assessment of the unit's involvement in training:

There is a good involvement of the team in student teaching, especially for master and medical doctors training. The team is actively involved in teaching and training in the field of urology and cancer. One of the group leaders is co-responsible of the physiopathology master 2 at Strasbourg University and is coordinating the teaching of oncology courses for medical doctor at the faculty of medicine.

# 4 • Grading

Once the visits for the 2011-2012 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 four criteria defined by the AERES and was given along with an overall assessment.

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

## ❖ Overall assessment of the unit :

**Cell signalling and communication in kidney and prostate cancer**

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont très bons.

## Grading table:

| C1<br>Scientific quality and production. | C2<br>Reputation and drawing power, integration into the environment. | C3<br>Laboratory life and governance. | C4<br>Strategy and scientific project. |
|---|---|---|---|
| A | A | A | A |

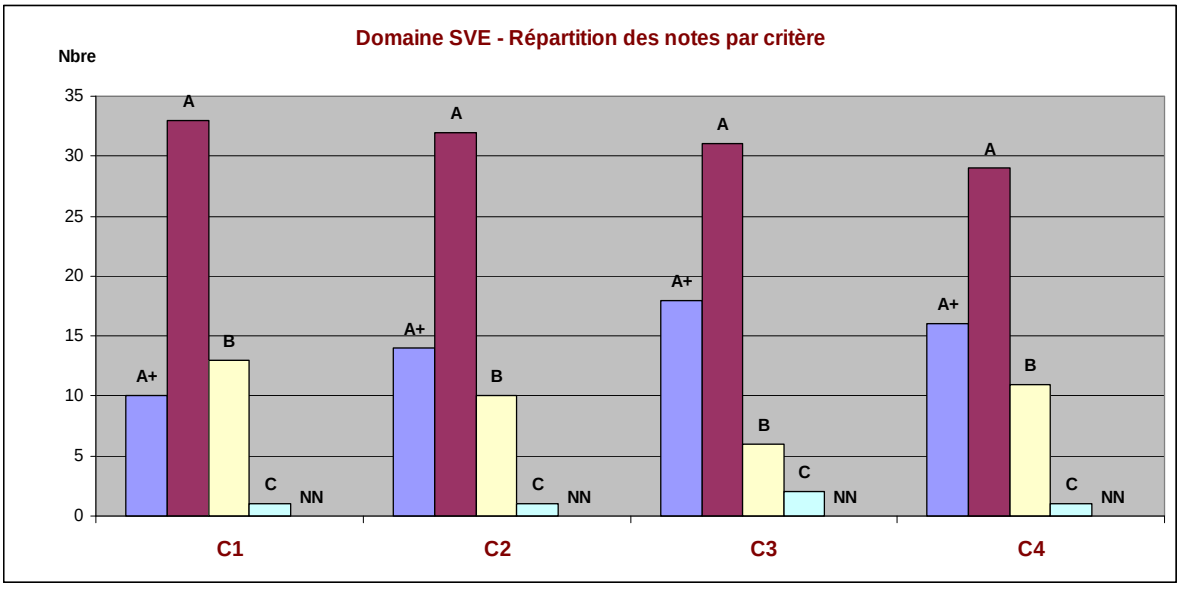
## 5 ● Statistics per field : SVE au 10/05/2012

**Notes**

| Critères | C2 | C2 | C3 | C4 |
|---|---|---|---|---|
| | Scientific quality and production. | Reputation and drawing power, integration into the environment. | Laboratory life and governance. | Strategy and scientific project. |
| A+ | 10 | 14 | 18 | 16 |
| A | 33 | 32 | 31 | 29 |
| B | 13 | 10 | 6 | 11 |
| C | 1 | 1 | 2 | 1 |
| Non noté | - | - | - | - |

**Pourcentages**

| Critères | C1 | C2 | C3 | C4 |
|---|---|---|---|---|
| | Scientific quality and production. | Reputation and drawing power, integration into the environment. | Laboratory life and governance. | Strategy and scientific project. |
| A+ | 18% | 25% | 32% | 28% |
| A | 58% | 56% | 54% | 51% |
| B | 23% | 18% | 11% | 19% |
| C | 2% | 2% | 4% | 2% |
| Non noté | - | - | - | - |



# 6 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de
l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

**Alain BERETZ**
Président

Strasbourg, le 6 mars 2012

Objet : Rapport d'évaluation du projet de l'UMR_S « Signalisation et communication cellulaires dans les cancers du rein et de la prostate » (réf. S2PUR130004559-RT)
Réf. : AB/EW/N° 2012-98

**Affaire suivie par**
Eric WESTHOF
Vice-président Recherche
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**Direction de la recherche**

Cher collègue,

Je vous remercie pour l'évaluation du projet l'unité mixte de recherche «Signalisation et communication cellulaires dans les cancers du rein et de la prostate » porté par Monsieur Thierry Massfelder.

Vous trouverez ci-joint les réponses du porteur de projet concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ

UNIVERSITÉ DE STRASBOURG

Par délégation du Président
de l'Université de Strasbourg
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**P.J. :**

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

**Unité 682 – Equipe 3**
Faculté de Médecine
Bâtiment 3 – 8ème étage
67085 Strasbourg Cedex
Tél : +33 (0)3 90 24 34 55
Fax : +33 (0)3 90 24 34 59

Strasbourg, February 27th 2012

**Object** : Observations concerning the AERES report on unit : "cell signaling and communication in kidney and prostate cancer" (Director: T. Massfelder) under the supervision of University of Strasbourg and INSERM (CSS4) – **Part II: "observations and responses"**

1. Page 5 of the report " Weaknesses and risks" and first part of the second paragraph of "Recommendations"
   As specified on page 3 of the report our wish is to develop an active fundamental, translational and clinical axis in urologic cancers priorities. The presence of an important hospitalo-academics staff in the team, with specificities in urology, oncology and pathology, is important to reach this goal. Moreover, it should be stressed that the hospitalo-academics staff will actively participate in research activities of the team.

   We completely agree that the retirement of Dr Mariette Barthelmebs (CNRS researcher) in 2014 will weaken the research potential of the team. To anticipate this potential lack of research resources we have 4 options that we will follow in terms of prospection for permanent positions according to the academic status of our team :
   - To present Dr Gaëlle Lapouge to INSERM or CNRS position in 2013, as precised in the last paragraph of page 6 of the report. Dr G. Lapouge was a former PhD student in Dr Jocelyn Céraline's group. She holds a post-doc position at the "Université Libre de Bruxelles", Belgium, since fall 2007;
   - To present Dr Valérian Dormoy as an associate professor (research) at the University of Strasbourg in 2013, as precised in the last paragraph of page 6 of the report. Dr V. Dormoy was PhD student in Dr Thierry Massfelder's group. He holds a post-doc position at the Irvine University, Irvine, Ca, USA since beginning 2011;
   - To present Dr Carole Sourbier to INSERM or CNRS position in 2014. Dr C. Sourbier was PhD student in Thierry Massfelder's group. She holds a post-doc position in the Onco-Urology branch of the NIH, Bethesda, MD, USA since mid-2007. This possibility does not appear in the report since Dr C. Sourbier recently

advised Dr T. Massfelder of her wish to come back to France to work with our group;
- To hire a new researcher through mobility; the procedure for such a possibility will be initiated in the near future through an add that will be posted at least in the INSERM and CNRS websites.

To further anticipate this potential lack of research resources of the future team, we will also pursue the option of hiring more post-doctoral fellows. This will be possible through application to ANR projects and to European grants; the various collaborations we already have and forthcoming contacts that will be developed at the national, European and international levels (please refer also to point 4 below) will allow us to go further in this direction. Partnership with industries as the ones that have already been set up and the ones that we intend to develop (please refer to point 2 below) could be another source of funding for post-doctoral positions. This is an important concern for the development of the team and we will put substantial efforts into this aspect.

2. Page 5 of the report "Recommendations" on the prioritization for the RCC part.
   As recommended by the members of the Committee of experts, we will focus this research on the sonic hedgehog (SHH)-Gli pathway and the Lim1 transcription factor in terms of involvement in tumor growth, invasion and resistance to therapies by both *in vitro* and *in vivo* approaches as presented during the visit of the Committee. In addition to this clear fundamental research in this field we also intend to :
   - Establish contracts with the pharmaceutical industry in order to develop partnership in the SHH inhibitors field at both preclinical and clinical levels. In this context, we have already identified Roche, Novartis, Affinity Pharma, Pfizer and Millennium as potential partners, since they have already developed Smo receptor inhibitors and have currently phase I or II clinical trials with these compounds for other pathologies;
   - To establish partnerships with chemists groups to develop chemical inhibitors of Lim1 transcription factors ideally at the nanomolar range or cationic siRNAs for translational and preclinical research and clinical applications. There are excellent chemistry laboratories locally, especially at the Faculty of Pharmacy, University of Strasbourg. Contacts have already been initiated for this purpose.

3. Page 5 of the report "Recommendations" on the use of specific transgenic mice to address more specifically the mechanistic basis of our finding.
   We completely agree with this recommendation, although it should be stressed that mice and rodents in general rarely develop kidney tumors as RCC or clear cell RCC (CCC, the main RCC sub-type) that mimic what is observed in humans. However, this is a very good recommendation that we will follow.
   For this purpose we have already contacted the "Institut Clinique de la Souris (ICS)" of the IGBMC (Illkirch, France) here locally (i) to find the appropriate conditional transgenic models allowing a spatio-temporal control of the expression of our transgene in the proximal tubules, from which CCC arises. We could develop a mouse model from the transgenic line "Tg(Kap-CreER$^{T2}$)" in which the expression of CreER$^{T2}$ is under the tight control of the *kidney androgen regulated protein* (Kap) promoter that is specific to early and late proximal-tubule cells. Thus, we will have the

opportunity to develop transgenic mice with specific and conditional deletions of the Ptch receptor, that is responsible for the intracellular sequestration and thus inactivation of the Smo receptor. In addition, by using such a promoter or the gamma-glutamyl transpeptidase-I promoter, that is also specifically expressed in proximal tubules of the kidney, it will be possible to constitutively activate the *Lim1* gene but also the *Smo receptor* gene in proximal tubules. We will go on this direction to assess the possibility that the generation of such transgenic mice will allow to develop models of kidney tumorigenesis. It should be stressed that transgenic models with conditional (or not) deletion of *SHH*, *Ptch* or *Smo* genes have been described in the literature, for studying for example their role in kidney nephrogenesis, but these models will not be adequate for our topic.

Von Hippel-Lindau proteins regulates the protein stability of HIF$\alpha$ and loss of VHL function, which is observed in > 70 % of sporadic CCC, leads to HIF stabilization leading to the expression of various angiogenic, proliferative or metabolic factors including VEGF, PDGF, TGFs and PTHrP, that have been shown to be involved in kidney tumorigenesis. Transgenic mice with *VHL* gene deletion have also been reported but neither the homozygous (which dies *in utero* mainly from vascular defects) nor the heterozygous mice develop CCC. In addition, conditional *VHL*-deleted transgenic mice in proximal tubules develop renal cysts but to date no evidence of the development of CCC have been described in these models.

Very recently, Gudas LJ et al. (PMID: 21908555) reported the generation of a transgenic mouse model of von Hippel-Lindau (VHL) renal cancer termed the TRACK model (transgenic model of cancer of the kidney), that specifically expresses a mutated, constitutively active HIF1$\alpha$ in kidney proximal tubule cells. In this model, kidney histologies are very similar to those of patients with VHL disease including multiple renal cysts and early onset of CCC. Whether this model may be used for studying the mechanistic basis of CCC as it appears in humans is not yet established, since HIF1$\alpha$ is not the only molecular entity to be involved in CCC. For this concern, we will contact Dr LJ Gudas for more details on this model and also to try to set up a collaborative work with his group to eventually support our findings, in the case their model may be useful for RCC and particularly CCC tumorigenesis studies.

All these tools and collaborative works that we are on the way to put in place, along with the models of urologic cancers that are developed by the start-up Urolead that we have created with the Urology Department, should clearly help us to specifically address the mechanistic basis of our findings in human RCC.

4. Page 5 of the report “Recommendations” on international collaborations that should be reinforced.

   As presented in the point 1 above, we have already developed various collaborations locally, nationally and at the European levels; some others are still under discussion for finalization especially at the European and international levels with groups involved in kidney development, with the group that has developed the TRACK model and with groups in NIH for comparison of our findings depending on the VHL status of RCC patients. For prostate cancer, the same policy will be followed concerning signaling pathways involved in response to androgen receptor variants that are constitutively activated and responsible of the hormone-resistance of prostate cancer patients.

Collaborations with the pharmaceutical industry will also be reinforced (please refer to the point 2 above) as well as local collaborations with chemists groups.
It should be stressed also that additional collaborations will be put in place in a reasonable way according to human resources of the team.

5. Page 5 of the report "Recommendations" on same localization of both original teams.
   Yes, clearly both teams will be located at the same site; this is of course very important. We have two options that will depend on timing.
   The INSERM building located at the site of the Strasbourg-Hautepierre Hospital along with the building of the "Fondation transplant" located close to this building will be the site of the teams working on cancer in Strasbourg. This will allow research teams working on cancer to be located near the future "Institut Régional du cancer (IRC)" of Alsace. Our team will be localized at this site and in the same laboratory at the end of 2012. If, for a question of timing, this solution will be available only after the beginning of the next five-year period, both original teams will be localized at the site of Dr Massfelder's group in the School of Medicine of Strasbourg, building 3, where there is enough room for all the staff (around 400 square meter). Thus, whatever the timing, both original teams will be localized at the same site at the beginning of the next quinquennat.

6. Page 6 of the report, "Assessment of scientific quality and production", third paragraph, on the following of the project on prostate cancer
   Yes, as recommended by the Committee, the research program on prostate cancer will be followed as presented.

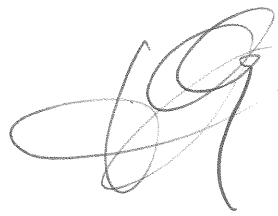
7. Page 6 of the report, "Assessment of scientific quality and production", sixth paragraph, on the international position of the team.
   Indeed, the international position of our groups is difficult to assess when looking at the number of invitations to international meetings.
   Since 2007 we have presented 27 abstracts and/or communications in national/European/ international congresses.
   Our recognition also comes from the facts that; we are reviewers in various journals; we participate in various types of expertise (for INSERM, Pasteur Institute in Paris, AERES, LNCC ...); we are members of scientific councils and boards (Dr T. Massfelder is for example a selected member of the SEQUOIA board: multidisciplinary reflexion group on sequential treatments in oncology coordinated by Prs B. Escudier and E. Raymond and Novartis); we are members of the organization team of local and European meetings (ESUR, EuCC); we have financing from various sources which means that our activities are recognized by various scientific councils; Dr T. Massfelder got the scientific prize of the FRM in 2010 (Alsace committee) and was recently invited as lecturer in the 2011 annual meeting of the American Society of Nephrology (Philadelphia, USA); Dr J. Céraline was invited to seminars on androgen receptors in Europe.
   All this is certainly not enough and our policy is to improve this point, as presented during the visit of the Committee. We will continue to present abstracts in French, European and international meetings to improve not only the recognition of the team but also invitations in these meetings as well as invitations to seminars around the

world. Collaborative works on the way to be set up will also help to reach this goal and will increase our attractiveness for post-doctoral fellows and researchers. This policy will give us a better international visibility.

8. Page 6 of the report, "Assessment of the unit's integration into its environment", second paragraph concerning grants
   We indeed obtained financial supports from various sources. To improve that point we will develop European and international grants through the development of a network in the field of onco-urology. This will be possible through the increase of our collaborations with European and international laboratories as well as industries.

Sincerely yours,

Thierry Massfelder



Dr Thierry MASSFELDER, PhD, HDR
INSERM researcher
Team 3 leader, INSERM Unit 682