Microenvironnement tumoral et thérapies ciblée

Rapport Hcéres

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

Research Units Department

AERES report on unit:

The Microenvironmental Niche in Tumorigenesis and Targeted Therapy

MN3T

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

Section des Unités de recherche

Le Président de l'AERES

Didier Houssin

Section des Unités de recherche

Le Directeur

Pierre Glaudes

Unit

Name of unit:	The Microenvironmental Niche in Tumorigenesis and Targeted Therapy
Acronym of unit:	MN3T
Label requested:	UMR_S
Present no.:	UMR_S682
Name of Director (2009-2012):	Ms Michèle KEDINGER
Name of project leader (2013-2017):	Ms Gertraud OREND

Members of the committee of experts

Chair:	Ms Corinne ALBIGES-RIZO, Grenoble, France
Experts:	Mr Martin HUMPHRIES, Manchester, United Kingdom
	Mr Carl-Philipp HEISENBERG, Klosterneuburg, Austria
	Mr Andreas FAISSNER, Bochum, Germany
	Mr Jean-Jacques FEIGE, Grenoble, France
	Ms Ruth RIMOKH, Lyon, France (representative of INSERM)
	Mr Denis VIVIEN, Caen, France (representative of CNU)

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)

Ms Catherine LABBÉ-JULLIÉ (INSERM)

Report

1 • Introduction

Date and conduct of visit:

The site visit took place on January 11th 2011 at the Centre Européen d'Etudes du Diabète building in the Hautepierre campus, a center located closed to the lab building. It was conducted by an international evaluation panel of 7 experts in the scientific fields represented by the evaluated unit. Two months before the visit, each committee member had received a report in English including the description of the work performed during the last four years and the proposed projects for the laboratory. 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. The evaluation took place under excellent conditions in a public session with presentations and discussions with the director, group leaders, scientific staff, technical and administrative staff, post-graduate and PhD students. It was followed by a debriefing time organized by the committee at the end of the session.

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

The current unit (MNT3) has almost the same composition as Team 2 from the current INSERM Unit 682 directed by Ms Michèle Kedinger. This unit was created in 2009 as the result of the fusion of 3 former teams, two located in Strasbourg (U682 and U575) and one located in Basel (Switzerland) directed by Ms Gertraud Orend, who was recruited in 2008 as a DR2 INSERM. The unit gathers 23 people. The organization of an independent unit (MNT3) for the next five year-contract (2013-2017) follows the retirement of Ms Michèle Kedinger and reflects limited interactions with the other teams forming U682. This new unit benefits from expertise about extracellular matrix and cell adhesion in development and disease in different organs (intestine, brain, pancreas, breast). The unit is focused on the role of the microenvironment and especially the impact of matrix stiffness on cell migration and angiogenesis in normal tissue homeostasis, inflammation and cancer progression. A continuum of research is proposed from the fundamental roles of tenascin in both angiogenesis and metastasis up to the generation of peptides targeting transmembrane receptors (neuropilin-1, integrin, semaphorin3A). These peptides could be potent tools in clinical applications to prevent tumoral angiogenesis and progression. This latter project has been the starting point of a spin-off company (MTP Therapeutics) with support from the regional innovative business incubator.

The unit is located in an INSERM building adjacent to the hospital allowing for supply of human samples, library set up and development of translational research. The unit has a marked and visible position in the national and international training program (cellular biology and physiology, neurosciences) in the roles of teachers or teaching program coordinator at the Universities of Strasbourg, Basel or Beyrouth. All researchers of the unit are involved in higher education.

Regional and industrial partnerships (MTP Therapeutics) have been established.

Management team:

During Ms Michèle Kedinger's direction of Unit U682 (about 70 people), the director was assisted by 2 secretaries. One of them will work for Ms Gertraud Orend's unit in the future. However institutional funding for the unit was shared between teams according to their needs and grants/external funding was raised by individual investigators.

The new research unit is governed by Ms Gertraud Orend who has already acquired management experience by leading a team in Basel and who will be assisted by a secretary, and 3 researchers responsible for computer tasks, communication and health/safety respectively. Even though each project leader is requesting external grants, acquired funding is shared within the unit. Technical personnel is allocated to the projects based on demand and expertise. Active discussions between unit members are performed at a weekly internal institute seminar. Once a month the strategy is discussed during an executive committee between members forming "the directive committee" consisting of the director, project leaders and permanent scientists.

Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	3	3
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	1	0	3
N4: Engineers, technicians and administrative staff * on a permanent position	3	7 [5.2]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2	3 ****	
N6: Postdoctoral students ***	2	3	
N7: Doctoral students	7	5	
N8: PhD defended	7		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	5	6	
TOTAL N1 to N7	**20**	**13 (24) ******	**9**

* **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.

*** Numbers according to form 2.7 of the unit`s application in June 30, 2011

**** Other personnel being present at 1. 1. 2013 is added to the shaded area and FTE of all personnel is presented in brackets.

2 • Assessment of the unit

Overall opinion on the unit:

The current unit aims to establish a monothematic research unit focused on the biological, biochemical and biophysical properties of the tumoral microenvironment and its associated signalling pathways through study on angiogenesis, cell dissemination and homing. The unit offers a good continuum of research from fundamental understanding of the role of tenascin-C in tumor development up to clinical applications of an original receptor-targeting strategy via amphiphilic peptides that supports highly promising therapeutic developments. The unit offers strong attractiveness as examplified by the potential integration of an ATIPE/AVENIR candidate with a strong CV and a highly relevant research program on the role of caveolin in this same research field. The visiting committee considers this intention as a vibrant addition to the unit. The Hautepierre building had already proven to provide an excellent infrastructure in terms of space and facilities (secretary office, animal facility, molecular and cell biology, cell and small animal imaging). Even though some applied projects are proposed, most projects remain in the field of basic research. The unit is promising and the relevance of the questions addressed is strong in the field of tumoral microenvironment, cell adhesion and mechanotransduction. The unit is led by a scientist who is well supported by the entire team. The unit is dynamic and well-balanced with an optimal combination of permanent researchers, postdocs and students. All expertise for pursuing the project is available within the team or through collaborations. Good expertise of senior scientists is documented in the field of microenvironment, cell adhesion molecules and animal models. Unit scientific production is good in terms of quantity and quality when evaluated in relation to the time required for restructuring a laboratory.

Strengths and opportunities:

The unit is based on a good expertise of senior scientists in the field of microenvironment, cell adhesion and tumorigenesis.

The development of original transgenic mouse models (KO, tissue-specific transgenesis) for the study of tenascin-C will represent the basis of the research program.

The use of spontaneous tumor models rather than subcutaneously grafted tumor cell lines is recognized as a scientifically sound decision and a valuable effort.

The development of an experimental strategy (patented and licensed to a spin-off company) allowing specific targeting of single transmembrane receptors (neuropilin-1, integrins, tyrosine kinase receptors…) and subsequent therapeutic applications is original and creative.

The attractivity of a very complementary project on caveolin headed by a young researcher should reinforce the unit.

The unit displays a clear ability to recruit talented young scientists, to raise funds through competitive grant applications, to develop productive collaborations and to maintain a good critical mass. Basic and translational researches are conducted, together with active collaboration with a biotech company for development of inhibitory peptides.

Weaknesses and risks:

The project is ambitious but the high number of animal models developed may be seen as a threat of remaining at the level of phenotype description without pushing forward the understanding of the mechanisms of action of tenascin and related ECM molecules in tumorigenesis (receptors, signalling pathways).

A qualified animal facility is available but the housing of a large panel of transgenic animals has to be checked.

The use of in vivo imaging such as MRI and PET-scan for small animals is lacking although efforts are under way to close this gap by adequate collaborations.

To avoid conflicts of interest, the project on transmembrane peptides used as therapeutic agents should be clearly distinct from the objectives of the spin-off company and focus on targets different from neuropilin-1 as proposed by the project leader.

Although, individual projects are of interest, collaborative projects and interconnectivity between research axes need to be well specified and reinforced.

All permanent scientists of the unit appeared to adhere to the leadership and scientific orientation of the Director. Some of them accepted to drop their long-term personal line of research to reinforce the workforce on tenascin-C. Still some additional efforts should be made over the next years to better interconnect the projects on tenascin-C and those on transmembrane peptides. The integration of an INSERM/AVENIR candidate would certainly help to create links between these two research projects. However, in the absence of the AVENIR/ATIP support and/or the expected arrival of the young investigator, the unit will lack expertise in mechanotransduction.

Invitations to top ranked meetings are missing.

Interactions with biophysicists need to be developed to maintain competitiveness.

Recommendations:

Given the idea to reinforce an interdisciplinary research environment based on animal models, animal imaging and biophysical studies for the future, further efforts are required to provide the basis for this very exciting concept. Unit members should more intensely communicate their results at the international level. An important recommendation is to submit and publish their results in higher impact journals, but also to increase the number of scientific presentations at international meetings. The unit needs a full support from all the institutions to decrease the teaching load of the more dynamic scientists with university commitments.

The unit has to improve its international visibility. To do that, the unit should identify a common scientific goal and establish priorities in its ongoing research with clear objectives to reach.

3 • Detailed assessments

Assessment of scientific quality and production:

The unit has worked on a dialog between cells and their surrounding extracellular matrix along 2 axes: (i) by elucidating the role of extracellular matrix molecules (tenascin-C) in cell migration and angiogenesis in normal homeostasis but also under inflammatory conditions and during tumoral progression and (ii) by targeting receptors involved in microenvironment-dependent signalling (neuropilin, integrins, semaphorin 3A, VEGFR) through generation of inhibitory peptides against the transmembrane domain with the aim to modify tumoral angiogenesis and progression. The unit has established several mouse and cellular models (KO and overexpression) to modulate tenascin-C expression in the microenvironment. Recent results obtained by the unit are the following:

-role of laminin in intestinal development and cancer: by RNA profiling, the unit showed that LM511 is regulating the PI3K/Akt signaling. The unit has shown the requirement of LM111 in eye development since the conditional deletion of LM111 leads to blindness, which is due not only to a defect in organization and composition of the retinal basement membrane, but also to an abnormal retinal vasculature. The requirement of LM1 in cortex development has been demonstrated whereas LM332 is involved in tumoral progression through perturbation of angiogenesis. Finally, some evidence shows the role of Laminin alpha1 and alpha5 in inflammatory bowel disease such as Crohn's disease and ulcerative colitis.

-role of tenascin in rheumatoid arthritis through Toll-like receptor 4 signalling by inducing pro-inflammatory cytokines and in tumor progression through Wnt signaling activation, and in the creation of a protective microenvironment and participation in lymph node mimicry-associated tumor evasion.

The unit has shown that a peptide mimicking the transmembrane domain of neuropilin 1 antagonizes the biological function of neuropilin and validated the antiangiogenic and tumor growth inhibitory effect in 3D assays and in preclinical mouse models of brain tumors (Oncogene 2010). Transmembrane peptides can also be used for live imaging of tumor progression.

The production of high impact publications has been hampered by the development and analysis of animal models which has been very time-consuming. The quality of internal publications is good since 44 publications have been accepted including 14 original publications (Cancer Research, Mol Biol Cell, Oncogene with a mean impact factor of 7.7 during the last past 4 years), 20 publications issued from fruitful collaborations (Nature Cell Biology, Nature Medicine, Journal of Cell Biology Small, Cancer Research…), 5 invited reviews, 5 book chapters and 3 editorials, 1 licensed patent. The unit has also successfully attracted grants (2 INCA, 3 ANR, Labex).

Unit members have been invited in 20 conferences (9 in France, 11 abroad).

Assessment of the unit's integration into its environment:

The INSERM building is physically located at the Hautepierre campus close to the Hautepierre Hospital, to the "Institut Regional du Cancer" and to the "Centre de Ressources Biologiques" which is in charge of providing biological specimens. The unit has demonstrated a good ability to raise external funding grants (3 INCA, 2 ANR, Medalis Labex) and grants based on national and international collaborations. Several collaborations with the clinics are allowed through INCA grants. The Labex Medialis, of which the unit is a founding member, will certainly help to foster the collaborations with pharmacologists. Valorisation of the research is quite impressive since a spin off has emerged from the translational research developed in the unit. Several conferences are scheduled with the involvement of unit members (Basel meeting on the tumor environment, 2nd meeting on targeting matrix in cancer, course on in vivo models in cancer for industry, NEUREX Symposium on cell migration in the brain, French society for matrix biology, FASEB conference on matricellular proteins).

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

The group leader enjoys national and international recognition but could be invited to more International meetings. She is very active through participations in numerous national and international calls.

Unit members have been invited to 20 conferences (9 in France, 11 abroad). The unit received the Universal Biotech Innovation Prize 2011 and 7 prizes including a "contrat d'interface", a "prix de la fédération pour la recherche sur le cerveau", an award from the European Association for cancer Research Applied Biosystems and distinctions for poster presentation and for excellent young researcher.

The unit has recruited its own team leader as an Inserm senior researcher (DR2), 4 post-doctoral fellows including 3 foreigners (India, Italy, United Kingdom). 7 PhD students from France and abroad are currently trained in the team. The unit is attractive for 3 advanced scientists want to join the team. The unit has been successful in recruiting an associated clinician who will strengthen the relationship with clinics. The head of the Neurosurgery department (University Hospital Strasbourg) will join this unit in January 2013 and therefore is included in the workforce. A talented young investigator is expected to join the research unit in summer 2012 by applying for an ATIP-AVENIR program.

In addition, the unit developed fruitful collaborations with numerous labs in France and Germany and the group leader has co-organized 6 scientific meetings in Strasbourg and a FASEB conference session in USA. All permanent scientists are involved in national (CNU, ANR) and international reviewing for grant agencies, scientific commission and scientific journals.

Assessment of the unit's governance and life:

The PI is German, offering international dynamics through the usage of English as the internal lab language. The proposed director of the unit appears to be well appreciated and respected by her colleagues. Not only charisma and expertise of senior scientists but also attractiveness towards young investigators and clinical researchers should contribute to the success of the unit. There is a good balance between staff scientists, technicians, post-docs and students. The possibility to attend international conferences is appreciated by post-docs and students. The technical staff is well supported in terms of training, preparation of competitive examinations and opportunity of recruitment in a spin off founded by one of the unit's scientists.

Assessment of the strategy and 5-year project:

The merging of the three original expertises in a monothematic research unit with an integrated fundamental and applied research program is highly relevant. The project is still focused on the interplay between cells and their microenvironment by (i) studying mechanical properties of extracellular matrix controlled by either extracellular matrix components (tenascin-C) or adhesion associated signalling pathways (integrins, neuropilin, caveolin); (ii) targeting central organizers of adhesive transmembrane receptor signaling (integrins, neuropilin-1, VEGFR, Semaphorin) with inhibiting transmembrane peptides. The goal is to understand the organization of the tumoral microenvironment, the modulation of physical and chemical properties of the tumoral microenvironment, the duality between non adhesive and adhesive extracellular components (tenascin-C versus fibronectin) leading to angiogenesis and metastasis and affecting drug responsiveness. Brain and breast cancer will be studied through experimental mouse, chicken and zebrafish models and through organotypic organ and 3D cell culture models (spheroids and biomaterials).

In a more global and academic approach, expression profiling (RNA, protein) will define matrix composition in WT tenascin-C, KO or overexpression conditions in order to reveal tenascin-C impact on matrix expression and organization, tissue stiffness (AFM, force maps of frozen tissue) and integrin signaling (including caveolin and neuropilin signalling). It will be addressed whether tenascin-C affects vascular integrity by focusing on tubulogenesis, pericyte coverage and pruning thanks to 3D collagen gels, hanging drops, bioengineered matrices, CAM assay and zebrafish angiogenesis model. The potential role of tenascin-C in the transdifferentiation of tumor cells into endothelial cells will be investigated in the orthotopic brain tumor model (glioblastoma xenografts). It will be studied whether tenascin-C matrix tubes can offer potential trafficking routes. Tumor angiogenesis will be addressed in the zebrafish model whereas the tumor metastasis, dissemination and homing will be analyzed in breast cancer NeuNT and PyMT mice. These complementary appoaches appear pertinent and competitive. The evaluation committee feels however that the unit should go far beyond the description of the phenotypes observed in these various biological contexts and attempt to decipher the molecular mechanisms (receptors, signalling pathways) by which tenascin-C mediates these distinct effects.
The unit has also developed these last few years an original approach to interfere with and thus to prevent the signalling pathways initiated by the recruitment of adhesion molecules during the processes of angiogenesis and metastasis. Briefly, they use a set of hydrophobic peptides targeting the transmembrane domains of receptors for adhesion molecules. By using these original tools, the unit is studying the influence of neuropilin and others actors in the control of tumor progression. Although some questions remain to be answered concerning the specificity of action of these peptides, their bioavailability in vivo or their targeting to tumor sites, the visiting committee has been convinced by the strong potential of these components as potential therapeutic agents. The committee recommends that basic research on the understanding of the mechanism of action of these peptides (the structural studies that have been initiated through collaborations in France shoud definitely be helpful in that sense) and on the improvement of their targeting should be pursued in the laboratory while the spin-off company MTP Therapeutics will

focus on the clinical applications. Also, the generalization of the concept established with neuropilin-1 to receptors of interest in the field of research of the laboratory appears as a valuable challenge.

On the basis of this peptide technology (licensed patents), the unit is developing a translational approach, in a cutting edge project in partnership with MTP Therapeutic.

Assessment of the unit's involvement in training:

The unit has a visible position in the national and international training program (cellular biology and physiology, neurosciences) as teachers or teaching program coordinator at the Universities of Strasbourg, Basel or Beyrouth since all researchers of the unit are involved in higher education. Strong implication in teaching activity and creation of a cell imaging platform on the Health and Sciences campus of Strasbourg University has been secured by positions affiliated to the university ensuring full time teaching duties.

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 :

The Microenvironmental Niche in Tumorigenesis and Targeted Therapy

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

Grading table:

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

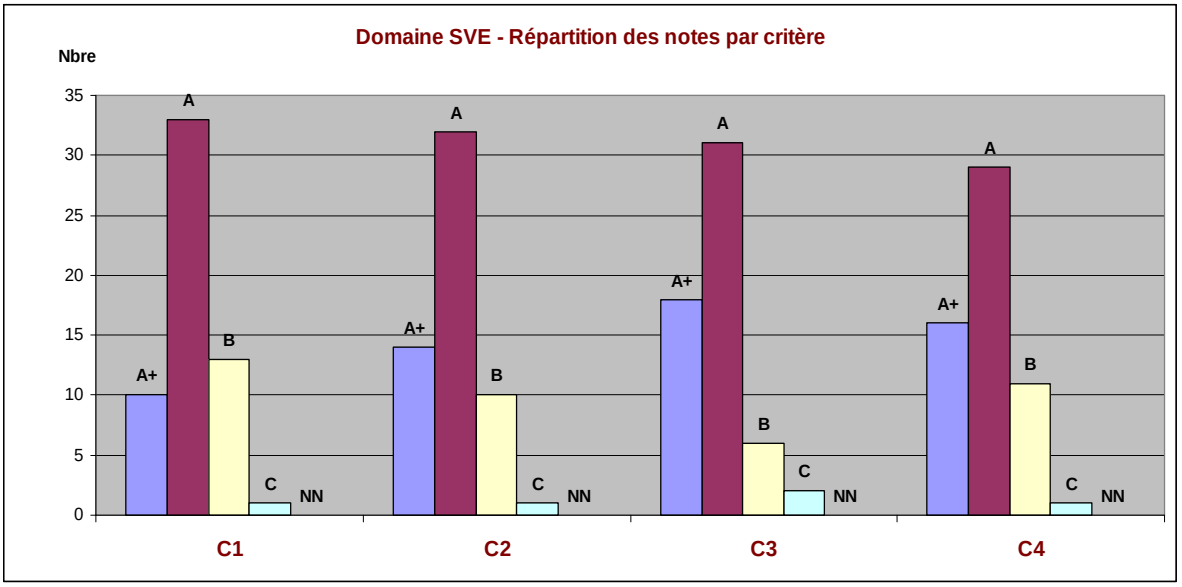
5 ● Statistics per field : SVE au 10/05/2012

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

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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 «Microenvironnement tumoral et thérapies ciblée » (réf. S2PUR130004552-RT)
Réf. : AB/EW/N° 2012-99

Affaire suivie par
Eric WESTHOF
Vice-président Recherche
et formation doctorale
Tél : +33 (0)3 68 85 15 80
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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation du projet l'unité mixte de recherche «Microenvironnement tumoral et thérapies ciblée» porté par Madame Gertraud Orend.

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

Par délégation du Président
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P.J. :

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

Inserm
French Institute
of Health and Medical Research

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To the AERES committee president

Comments to the AERES report for the MN3T unit "The Microenvironmental Niche in Tumorigenesis and Targeted Therapy"

We are grateful for the very positive evaluation and constructive recommendations made by the AERES committee and would like to comment on a few points.

- **It was mentioned that the unit should improve its international visibility. "The group leader...could be invited to more international meetings. An important recommendation is.....to increase the number of scientific presentations at international meetings".**

The current team enjoys considerable international visibility as evidenced by attracting over the past 4 years several foreign students (5), postdocs (2), and sabbatical scientists (5) with 7 different nationalities. Team members have organized meetings or sessions at meetings with international participants (5), presented research results at 20 conferences upon invitation (9 in France, 11 abroad), and delivered more than 50 presentations overall, including talks at Gordon Research and Faseb conferences. Presentations of seminars in research institutes (2 in France and 5 abroad), extensive reviewing for international funding agencies in Switzerland, Israel and USA, participation in PhD and habilitation committees in the UK, Germany, Switzerland and Austria, expert appraisal for several journals and serving as founder and chief editor of the journal "Cell Adhesion and Migration" (which is indexed with an anticipated impact factor of 4.6) has further increased international recognition. Moreover, researchers have obtained international prizes (including the Universal European Biotech Innovation Prize 2011) and are continuing to organize international meetings and sessions in the future (e.g. Neurex workshop 2012, Faseb Research conference 2013).

- **The committee has recommended that the research should be more focused and integrated and should extend on the identification of the molecular mechanisms. "Still some additional efforts should be made over the next years to better interconnect the projects on tenascin-C and those on transmembrane peptides".**

Since our creation in 2009 following the fusion of three teams with different but complementary expertise we have initiated projects with an integrated nature (supported by extramural funding). Further integration will be intensified in the future. We already strengthened this effort by reorienting the research program (e.g. discontinuing gastrointestinal tumor models). The future unit will focus on the role of the microenvironment on tumor angiogenesis and metastasis. Tenascin-C has been chosen as a cancer relevant extracellular matrix molecule. Biophysical and biochemical mechanisms of a tenascin-C-enriched microenvironment will be determined. Moreover perception of signals from a tenascin-C-enriched microenvironment by the cells through transmembrane receptors will be elucidated at the molecular level. Knowledge about signal integration from the tumor microenvironment is already used for the design and application of novel peptides targeting the transmembrane domain of cancer relevant adhesion and signaling receptors. This feedback approach provides a strong interconnectivity between the tenascin-C- and peptide-based parts of the project.
Our publication record on the identification of molecular mechanisms of tenascin-C (e.g. Lange et al., 2007, 2008) and the mode of action of the transmembrane targeting peptides (Hubert et al., 2010) reveals that our research has been molecular and mechanism-driven in the past and this will continue to be a focus for the future.

- **"The integration of an INSERM/AVENIR candidate would certainly help to create links between these two research projects. However, in the absence of the AVENIR/ATIP support and/or the expected arrival of the young investigator, the unit will lack expertise in mechanotransduction".**

The arrival of a young talented and competitive expert in biomechanics will indeed provide an integrative potential. Nevertheless, the staff scientists are experts in adhesion signaling and cover biomechanical aspects. Even if the ATIP/AVENIR candidate will not join the unit (immediately) the program is unique, innovative and competitive. The program will discover important information about signals from the tumor microenvironment relevant in driving angiogenesis and metastasis and will continue to translate this knowledge into the development of novel transmembrane peptides for targeting and live imaging of cancer.

- **It was mentioned that "...housing of a large panel of transgenic animals has to be checked."**

Very recently, the current team (future MN3T unit) was successful in acquiring financing through the Labex Medalis program for a new caging system that will quadruplicate the current capacity thus covering the anticipated needs.

- **It was noted that "The use of in vivo imaging such as MRI and PET-scan for small animals is lacking although efforts are under way to close this gap by adequate collaborations." Moreover, "Interactions with biophysicists need to be developed to maintain competitiveness".**

Through the Labex Medalis program where MN3T is a founding member we will obtain access to MRI and PET-scan in the frame of the TransImaging Equipex program that has been selected by ANR. Moreover, several collaborations with biophysicists have already been established which are supported by 2 collaborative grants (ANR, INCa, G. Orend coordinator) and a co-supervision of a PhD student by a physicist.

- **It was mentioned: "To avoid conflicts of interest, the project on transmembrane peptides used as therapeutic agents should be clearly distinct from the objectives of the spin-off company and focus on targets different from neuropilin-1."**

A distinct focus will certainly be given. Whereas MN3T will focus on the molecular mechanisms of action of selected transmembrane peptides, the company MTP Therapeutics will deal with aspects of ADME and strategies for translation as e.g. clinical trials, thus providing a non-competitive win-win situation for both entities.

- **"An important recommendation is to submit and publish their results in higher impact journals"**

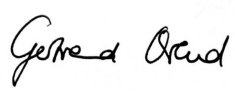
Stochastic transgenic and knockout cancer models with up to half year delay of tumor development have been used in the past and will continue to be used in the future which is a well appreciated but time consuming endeavour. Moreover, physical translocation to U682 had significantly delayed mouse breeding and experiments. Nevertheless, several manuscripts with a high publication potential are in preparation or are in the submission/resubmission phase. Accepting the associated delay our declared aim is the publication of complete and comprehensive data in higher impact journals, rather than publication of only single aspects in lower impact journals. Publications in higher impact journals will also further increase invitations to international conferences.

- **"The new research unit is governed by Ms Gertraud Orend who has already aqcuired management experience by leading a team in Basel..."**

The team leader has obtained more than 9 years of experience in leadership both in Basel (5 years) and in Strasbourg (more than 4 years).

Sincerely yours,

Gertraud Orend



Strasbourg, 7. 3. 2012