Validation et identification de nouvelles cibles en oncologie

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

VINCO INSERM U916

From the

University Bordeaux 2

INSERM

The Institut Bergonié

May 2010

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The Institut Bergonié

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: VINCO

Requested label: UMR_S INSERM

N° in the case of renewal: U916

Name of the director: Mr Josy REIFFERS

Members of the review committee

Chairperson :

M. Jean-Paul BORG, Marseille

Other committee members:

M. Sakari KNUUTILA, Haartman Institute and HUSLAB, Helsinky, Finland

M. Oreste SEGATTO, Regina Elena Cancer Institute, Rome, Italy

M. Robert ZEILLINGER, Medical University of Vienna, Austria (absent)

Committee members nomminated by staff evaluation committees:

M. Xavier COUMOUL, member of INSERM CSS

M. Olivier OUDAR, CNU member

Observers

AERES scientific advisor:

Mrs Marie-Annick BUENDIA

University representatives :

M. Manuel TUNON DE LARA, University Bordeaux 2

M. Alain BLANCHARD, University Bordeaux 2

Research Organization representatives:

Mrs Lucie BESSE, INSERM

Mrs Catherine LABBÉ-JULLIÉ, INSERM

Report

1 • Introduction

- Date and execution of the visit

The visit took place at Institut Bergonié on November 25th, 2009. After a general presentation by the Director and the Deputy Director, three scientific programs (hereafter named projects #1-3) were presented to the visiting committee in the morning. In the afternoon, after discussion with the representatives of Inserm and the University, the visiting committee was split into three groups that met behind closed doors with engineers, technicians, administration personnel, PhD students, post-docs and tenured scientists. The visiting committee met afterwards to comment on the research programmes and organization of U916 VINCO.

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

The VINCO research unit is located within the compound hosting Institut Bergonié, the Bordeaux cancer center located in downtown Bordeaux. VINCO was created on January 1st, 2008 to merge pre-existing INSERM research teams based in Bordeaux. Scientific activities are focussed on clinical, translational and fundamental research mainly in the field of sarcoma and breast cancers. The VINCO unit is hosted in a 900 square meters research facility. A new research area of 500 square meters is due to be completed by 2013.

- Management team

The Director of the Unit is assisted by a recently appointed Deputy Director. A so-called Bureau is composed of 7 senior investigators, including the two pre-cited persons in addition to five investigators with permanent positions.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	17	18
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	8	10
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	8
N7: Number of staff members with a HDR or a similar grade	15	16

2 • Overall appreciation on the research unit

- Overall opinion

Unit 916 is organized as a single team INSERM research Unit. All programs are strongly oriented towards translational programs in cancer research. The main focus is on sarcomas and breast cancers. These are extremely relevant pathologies, whose clinical management at the Institut Bergonié is pursued with standards that have earned the Institute a solid nation-wide reputation. As stated in its denomination, Unit 916 centers its activity on the identification and validation of new targets in oncology. The work pursued by the Unit is competitive. Its originality will certainly be improved by the recent recruitment of outstanding PIs. A definite plus is the capacity of the unit to rapidly transfer basic science knowledge (in particular validated genomic signatures and cell-based assays) to clinical and industrial applications. The committee was impressed by the capacity of the research team to develop genomic screens aimed at improving the clinical management of sarcomas and breast cancers, and to produce and extensively validate very high quality data in these fields. Technological developments and industrial transfer (including patenting and creation of of companies) are very good. The major scientific weakness is the lack of in house expertise for the intensive pre-clinical validation of potential therapeutic targets emerging from genomic screens. The unit should therefore plan on strengthening its competence in the fields of cell biology and cell signaling. Moreover, an independent bioinformatics research group needs to be established within the Unit. Failure to do so would prevent the full exploitation of the incredible amount of data being generated by genomic screens.

- Strenghts and opportunities

A very competitive asset in the Unit is the availability of an impressive collection of biological material, especially in the sarcoma field (more than 300 sarcomas as well as 21 sarcoma cell lines fully annotated at the CGH and transcriptomic level). These biobanks have been built over the years in collaboration with experts in the field at the regional, national and international levels. These resources are yet to be fully exploited and therefore represent a unique opportunity for future developments. The Unit also benefits from strong clinical collaborations, which are rapidly translated into genetic studies. In fact, this team is a rather impressive example of how a « From bench to bedside » approach should be implemented. Excellent collaborations among scientists and pathologists. Patenting is good in the Unit and there has been the creation of spin-off companies where PIs are still involved.

- Weaknesses and threats

The Unit has the ambition to pursue a highly competitive research. Most emphasis is placed on descriptive genomics (CGH, transcriptomics profiling), which is unlikely to be enough to stay ahead of the competition in future years. Bioinformatics and molecular cell biology need to be boosted through a competitive hiring policy. It is unclear whether this will be feasible in the near future. There is excellence in house expertise in the field of high throughput cell-based assays. However, most of the work of this group is centered on the design and innovation of technological platforms in collaboration with spin off companies. It is odd that this expertise is not exploited for setting up high throughput RNAi and chemical genetics screens, which could be an excellent complement to descriptive genomics. The visibility of the unit is less than adequate. INSERM is not sollicited to hire high profile candidates and futur group leaders.

- Recommendations to the head of the research unit

- To catalyse the unification of cancer research in the Bordeaux area with help from Universités and ITMO Cancer.

- To increase the visibility of the Unit: website, organization of international meetings and workshops, vigorous programme of extramural seminars

- To develop an independant bioinformatic group to take full advantage of the amount of produced data (deep analysis)

- To develop a more agressive program of educational activities for PhD students, post-doc and also for PIs (external seminars, organization of congress & workshops).

- To develop selected mouse models for preclinical validation on specific programs (e.g. TRIO)

- To implement a vigorous policy aimed at attracting and hiring new PIs (competitive calls when new lab space available). Hiring INSERM (or CNRS) staff is a plus-value for research Unit that should considered in parallel to University staff recruitment depending on the profile of the candidate. One major point would be to increase the critical mass of scientists and resources devoted to basic science.

- To encourage and anticipate the emergence of independent teams and new leaders within the staff already operating in the Unit. Moreover, competitive calls should be implemented when new lab space is available.

- One major point would be to develop an independent bioinformatic group to take full advantage of the amount of produced data (deep sequencing is proposed in future projects and obviously more data will be generated!) with a significant number of PIs

- To improve collaborations and cross fertilization among geneticists running the technological platform presented during the visit and the sarcoma and breast cancer groups (clinical research) with the help of the vice-director

- Data on the work produced

A1:Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	11
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	10
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	11/13
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	10

3 • Specific comments on the research unit

- Appreciation on the results

This unit is organized as a single team. All programs are strongly oriented towards translational programs in cancer research. Two major focuses are sarcoma and breast cancer programs that are major public health problems and strong and recognized clinical activities at the Institut Bergonié. As announced in the title of Unit 916, identification and validation of new targets in oncology are major focuses. Originality does not really stand in the identification of molecular signatures (CGHa, transcriptomics) with prognostic value that are developped elsewhere or in the process of validation. Originality is strong in the fast building of the unit with the recent arrival of new researchers from the clinical, translational and fundamental fields, and the capacity of the unit to rapidly transfer basic science knowledge (in particular validated signatures, cell-based assays) to clinical and industrial applications.

The committee found strong relevance and very high quality and high capacity of the unit in identification and validation of molecular signatures in sarcoma (National reference Center, more than 1000 sarcomas banked in situ with careful clinical annotations, competitive networking of resources and knowledge at the national and international levels) and less in breast cancers where competition is much stronger and originality of the program is less convincing. All together, the Unit has demonstrated an impressive capacity to develop genomic and clinical programs in sarcoma and breast cancers, and to produce and extensively validate very high quality data in these fields.

Group 1 with very strong clinical and genomic expertises, presented high quality data on a prometastatic signature found in sarcoma under review in Nature Medicine (CINSARC). Moreover, a Phase 0 clinical trial on MDM2 inhibitors in a subset of sarcomas (sponsored by Roche and based on proprietary work of the Unit) is under way.

Group 2 presented work aimed at modelling breast cancer via the introduction of defined genetic lesions in primary mammary cells. This is done by combining lentivirus-mediated transfer of oncogenes as well as shRNAs targeting tumour suppressors. This project will be fully operational when the L3 lab under construction opens in 2010. Ideally, this project should provide the cultural and technological framework necessary for putting cancer genomics into a cell biology context. At present, however, the real potential of this approach, i.e. its usefulness for the effective modelling of breast cancer subtypes without resorting to mouse genetics, is not fully clear.

Group 3 develops cutting-edge technological platforms for fully automated high content cell-based assays. Importantly, two spin-off companies devoted to the commercial exploitation of these platforms have been launched by VINCO scientists. This group is not well integrated with the sarcoma and breast cancer groups (it uses other cancer tissues), although it is clear that its expertise would be extremely advantageous for setting up functional genomics projects.

Very good but not outstanding track of publications in the field of genomics & clinical research & methodological approaches (although Nature Medicine in revision, Nature Methods 2009), good in the field of basic science with recent high impact factor journals. Moreover, scientific communications are very active in the field of clinical research due to the very good international reputation of clinicians, much less in the field of basic science. The Research Unit is pretty good for patenting with industrial and technical achievements. There is a considerable amount of teaching activities in the field of clinical and translational oncology, much less in basic science.

Very good in the field of sarcoma: strong academic & industrial partnerships, apparently easy access to early clinical development of drugs. The major academic partners are European Network in sarcoma (CONCATINET), Canceropole GSO (tumor bank), EORTC in the field of clinical trials in breast cancers (head: Pr Bonnefoi). The main extra-european collaboration of the Breast Cancer group is J. Nevins's lab (US).

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

No major prize or scientific distinctions. There is regular participation of U916 members to national and international meetings (posters, oral presentations for a limited number of PI).

Two high profile members from Switzerland have joined the breast cancer groups to reinforce the unit (one Chaire d'Excellence Université de Bordeaux 2 for one of the two PIs). The research unit has started to build a bioinformatics group which is particularly relevant in regard to the impressive amount of data produced here. There is not yet a secured position for the leader (post-doctoral fellow) and the bioinformatic team (one M2 and one PhD students will be soon recruited). It is absolutely clear that there is a strong need to strengthen this lab/core facility (grants, students,..). The Direction did not express a real willingness to use available competitive calls (AVENIR/ATIP programs,…) to increase the number of top scientists in the Unit.

The Visiting committee was impressed by the ability of PIs (mostly 4 of them) to raise competitive funds from national and international agencies (INCA, ANR, EU, PHRC) and industrial partners was excellent.

Excellent collaborations in the field of sarcoma and breast cancer (very stable with EORTC and with pharmaceutical companies including on specific clinical research programs (ROCHE and Nutlin, MDM2-p53 inhibitor).

The "valorisation" part is excellent. There has been the launch of two spin-off companies in which PIs of the unit are still participating. Three patents have been filed under the name of PIs of U916.

- Appreciation on the strategy, governance and life of the research unit

The committee considers it as a strength that the unit is organized as a single team, rather than as a regular structure according to the INSERM "guidelines" (i.e. with independent teams or groups). Their organization is rationale according to their research's goals aiming to transfert clinical questions (management of sarcoma and breast cancer patients) to experimental designs, and go back to the bedside with innovative clinical trials.

After discussion with all categories of personal of the unit, the committee did not detect major conflicts among PI and/or PhD/Post-doc students.

There are regular lab and data meetings, and it is a good choice to have created an assistant-director position in close contact with scientific problematics. During discussions with technicians involved in both clinical and scientific duties (Institut Bergonié's personal), complains were voiced concerning a lack of communication between this category and the rest of the Unit. There is no lab council in the Unit.

Cancer is an emerging field in Bordeaux and there is a lack of visibility of the research unit at the national and international level. Institut Bergonié and U916 VINCO have the strength and the reputation required to act as the driving force of a major boosting of experimental oncology in the Bordeaux area.

The committee encourages the Unit to catalyse the emergence of future group leaders (and thereafter creation of INSERM teams). This is also particularly important for the renewal of the staff (in regard to future retirements for the next quadrennial, …). It did not appear a clear strategy to decide when to take risks on projects and how to gather a sufficient scientific, medical and technological task force to take the risk. As an example, it would be interesting to focuse on some interesting projects and take risk in developing the TRIO project using alternative models to those proposed, e.g. the generation of transgenic mice.

There are no intramural training programs focussed on experimental oncology available to PhD students working in the Unit (Doctoral school).

Professors and assistant-professor are associated to the teaching activities of the Université de Bordeaux 2.

- Appreciation on the project

The committee agreed on the high degree of feasibility of the clinical, genomics and technological projects. People are well trained, highly qualified, and are very competitive in regard to their research programs. Clinical studies are conducted in excellent conditions.

A pressing recommendation concerns the need to build a strong bioinformatic group (with independent scientific activities) based on tenured positions. The prospective group leader in Bioinformatics, appears to be competent although her position is not yet fully tenured.

The ability to generate large datasets is not associated to an adequate capability to pursuing biological and biochemical studies (let alone the generation of mouse models) aimed at clarifying the impact of genetic lesions discovered in tumours on cellular programmes and functions. This limits the capability of the Unit to test experimentally the hypothesis generated by discovery-driven research. This is an obvious and not trivial limit to the full pre-clinical exploitation of proprietary research projects.

The committee recommends that the unit invest more on basic science, cell biology and biochemistry to meet the scientific goals of the unit: validation of therapeutic targets in oncology. In term of long term basic science, the program should be more focused on selected projects (e.g. TRIO,..) and expand some experimental strategies (miRNA, animal models). Arrival of new teams in the U916 brought very strong emphasis on new biological problems, including stroma-tumor interactions, that will need new expertises (immunology, inflammation) in basic science.

No major concerns have been raised during the meetings with the members of the unit.

The Unit could improve the originality of the projects focusing on the implication of the new signaling pathways that were identified in recent studies (as examples: TRIO, unknown genes of the prometastatic signature). In contrast, projects on highly competitive signaling pathways such as NFkB and mTOR did not appear highly original and competitive.

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

Monsieur Pierre GLORIEUX
Directeur de la section Unités de recherche
AERES

Bordeaux, le 13 avril 2010

Monsieur le Directeur,

Je vous transmets les observations de Monsieur Josy REIFFERS, Directeur de l'Unité Inserm 916 «Validation et Identification de Nouvelles Cibles en Oncologie», faisant suite au rapport du Comité de visite de l'AERES.

Je vous prie de croire, Monsieur le Directeur, à l'assurance de mes sincères salutations.

Le Vice-Président du Conseil Scientifique,

Alain BLANCHARD

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OBSERVATIONS

Thank you for sending me the AERES report on INSERM unit 916. I note the broadly positive tone of the report and thank the reviewers for their detailed and constructive comments.

1. Bioinformatics
We fully agree with the committee's recommendation that bioinformatics be strengthened. We have hired a bioinformatician with the remit to form an independent bioinformatics group, and are actively exploring all possibilities to convert her post to a tenured position, including applications to the research councils and University.

2. Cell biology
We fully agree with the committee's recommendation that cell biology be strengthened and focused on testing new signalling pathways and new biological problems identified in the genomic studies at the institute. To promote cell biology we have created a P2 lab and are constructing a P3 lab on the Bergonié site. These facilities will be used to model the defects discovered by the genomics programmes. We will work with the University genomics platform and local startup companies to increase the use of RNAi and chemical genetics screens within the unit. The lack of large scale transgenic mouse facilities in Bordeaux makes it unrealistic to embark on major transgenic mouse projects, but we are committed to increasing our use of orthotopic xenograft models.

3. Hiring
We welcome the advice to solicit INSERM funding for new research groups at the institute, in particular in bioinformatics (see above) and cell biology. While waiting for this process to run its course, we are pleased to note that cell biology will be greatly strengthened in the short term by the arrival of a senior PI from the Curie Institute who will work on sarcomas and by the arrival of a post-doc to perform RNAi screens who will in due course apply for an INSERM junior scientist position.

4. Visibility
The French section of our website has been completely renewed in the last 12 months. We are committed to increasing the visibility of the institute by further development of the English language section of the website, by hosting more extramural seminars and by organising more international workshops. We also recognise the need for the institute to take the lead in raising the profile of cancer research in Bordeaux and will work together with our academic and clinical colleagues in the region to achieve this aim.

5. Doctoral programme
We will work with the doctoral school at the University to increase the relevance of the educational activities in experimental oncology for our PhD students.

Yours sincerely,

Josy REIFFERS.