MINT - Micro et nanomédecines translationnelles

Rapport Hcéres

HCERES

High Council for the Evaluation of Research and Higher Education

Research units

HCERES report on research unit:

Micro et Nanomédecines Biomimétiques

MINT

Under the supervision of the following institutions and research bodies:

Université d'Angers - UA

Institut National de la Santé et de la Recherche Médicale – INSERM

Centre National de la Recherche Scientifique - CNRS

Evaluation Campaign 2015-2016 (Group B)

HCERES

High Council for the Evaluation of Research and Higher Education

Research units

In the name of HCERES,[1]

Michel COSNARD, president

In the name of the experts committee,[2]

Karim AMIGHI, chairman of the committee

Under the decree No.2014-1365 dated 14 november 2014,

[1] The president of HCERES "countersigns the evaluation reports set up by the experts committees and signed by their chairman." (Article 8, paragraph 5)

[2] The evaluation reports "are signed by the chairman of the expert committee". (Article 11, paragraph 2)

Evaluation report

This report is the sole result of evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial reviewing by the committee.

Unit name:	Micro et Nanomédecines Biomimétiques
Unit acronym:	MINT
Label requested:	UMR
Current number:	1066
Name of Director (2015-2016):	Mr Jean-Pierre BENOIT
Name of Project Leader (2017-2021):	Mr Patrick SAULNIER

Expert committee members

Chair:	Mr Karim AMIGHI, Université libre de Bruxelles, Belgique
Experts:	Mr Hervé KOVACIC, Université Aix-Marseille (representative of the CNU)
	Ms Emmanuelle MARIE, ENS Paris (representative of the CoNRS)
	Mr Pierre MARQUET, CHU Limoges (representative of the CSS INSERM)

Scientific delegate representing the HCERES:

Mr Jean-Marie ZAJAC

Representatives of supervising institutions and bodies:

Ms Chantal LASSERE, INSERM

Ms Annabel LE LIDEC, INSERM,

Mr Christian PILLET, Université d'Angers

Ms Isabelle RICHARD, Université d'Angers

Ms Alexa ROUEZ, Université d'Angers

Mr Jean-François TASSIN, CNRS

Head of Doctoral School:

Mr Joël EYER, Doctoral school ED N° 502, "Biologie Santé Nantes Angers"

1 • Introduction

History and geographical location of the unit

The unit INSERM U1066 "Micro et Nanomédecines Biomimétiques" MINT was created following the merging of three structures (Pharmacie Galénique, Biophysique Médicale et Biophysique Pharmaceutique) in the late 90's. In 2004, the unit became the INSERM unit U646 «Ingénierie de la Vectorisation Particulaire». In 2012, the unit was reconducted as the Inserm UMR 1066 MINT (Micro et Nanomédecines biomimétiques) under the supervision of Mr Jean-Pierre BENOIT.

Since 2012, the MINT unit is located at the CHU of Angers in a new building (Institut de Biologie en Santé). This building gathers 8 laboratories and 5 technical platforms, forming a federative research structure named "Interactions cellulaires et applications thérapeutiques". The MINT infrastructures are located at the 3rd floor of the building and have a total surface of 1130 m².

Management team

The MINT unit is currently headed by Mr Jean-Pierre BENOIT. For the next contract, Mr Patrick SAULNIER will lead the laboratory.

HCERES nomenclature

SVE

SVE1_LS5

SVE1_LS3

Scientific domains

The MINT unit is involved in the development and physico-chemical characterization of molecular assemblies (i.e. pharmaceutical vectors) aimed to transport and deliver one or several active compounds to a target site. All the steps from the conception to the pre-clinical evaluation of the developed pharmaceutical vectors are performed using the know-how and the facilities available in the unit.

Unit workforce

Unit workforce	Number on 30/06/2015	Number on 01/01/2017
N1: Permanent professors and similar positions	18	15
N2: Permanent researchers from Institutions and similar positions	2	2
N3: Other permanent staff (technicians and administrative personnel)	9	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	6	
N6: Other contractual staff (technicians and administrative personnel)	4	
N7: PhD students	28	
TOTAL N1 to N7	**67**	
Qualified research supervisors (HDR) or similar positions	14	

*Estimated number of PhD student at 25/01/2016 according to the number of student currently in the unit. This number should be increased by at least 10 new ones, to be hired according to upcoming contracts.

Unit record	From 01/01/2010 to 30/06/2015
PhD theses defended	26
Postdoctoral scientists having spent at least 12 months in the unit	14
Number of Research Supervisor Qualifications (HDR) obtained during the period	1

2 • Overall assessment of the unit

Introduction

The MINT unit has developed its research in the field of the technology for health, with the development and preclinical testing of new formulations of known pharmacological medicines to improve their absorption, stability and overall effects. The unit is mainly focusing on the formulation of molecules applied to the treatment of cancer (glioblastoma and pulmonary cancer) and the formulation of microspheres encapsulating therapeutical proteins, acting as pharmacologically active microcarriers (PAM), which permitted to enhance the survival, differentiation and regenerative potential of mesenchymal stromal cells for application in tissue repair and regeneration. The pharmaceutical vectors are developed to transport and deliver one or several active compounds to a target site at a given time and during a period of time. Since 2012, the MINT unit focused on two research axes:

(i) Nanomedecines for cancer therapy: lipidic nanocapsules (LNC) are obtained by temperature induced phase inversion method in the absence of organic solvent. This rapid and robust process was developed in the 90's in the MINT unit. The LNC formed are now well characterized and used by clinicians for the treatment of several cancers. During this period, researches were focused on the development of a formulation platform enabling the encapsulation and controlled release of different drugs (anticancer drugs, radiopharmaceutics, siRNA, DNA, peptides and polysaccharides) and the functionalization of the surface of the vectors for applications in cancer treatment (glioblastoma, bronchial cancer). Both passive targeting (through EPR effect) and active targeting (peptide NFL-TBS.40-63) have been considered. More recently, the oral route has been considered as an alternative to IV injection. To enhance the biodistribution of the nanovectors in vivo, their diffusion in the gastric mucus has to be optimized. Therefore theoretical as well as experimental studies are in progress.

(ii) Microparticles for tissue engineering: The MINT unit has developed in parallel biodegradable and biomimetic microparticles able to encapsulate and release therapeutic proteins such as growth factors. These microparticles consisted in poly-lactide-co-glycolide acide (PLGA) copolymers or calcium carbonate and are obtained using supercritical CO_2 based techniques. The development of in situ measurement apparatus (for instance: pendant-drop tensiometer, Xray diffusion and diffraction, ...) allowed to address the question of the cristallisation of $CaCO_3$. Bioactive proteins, such as trophic factors, have been successfully encapsulated in PLGA microspheres. These objects are called MAP (pharmacologically active microcarriers) and can be used as 3D support for cell cultures while delivering active compounds. This has been used to prepare brain implants especially for the treatment of neurodegenerative diseases. In this field, the choice of cells and ex vivo models was shown to be of crucial importance.

All the steps from the conception to the pre-clinical evaluation of the developed pharmaceutical vectors are performed using the know-how and the facilities available in the unit. Moreover, the conception of the new pharmaceutical vectors follows the QbD (Quality by Design) approach, taking into account all the risks implied by the production process and their subsequent use in vivo. The restrictions linked to biopharmaceutical aspects such as administration route, toxicity and biodistribution are evaluated beforehand. The use of organic solvants is avoided to limit their potential toxicities and acceptable excipients for human use are preferably selected in the developed formulation. The laboratory is currently asking for an ISO 9001 certification.

For the next contract, the group developing the work on radiopharmaceutics and cancer will leave the unit and two groups will join the MINT unit: a small group of pharmacologists and a group from the neurobiology and transgenesis laboratory (EA 3143, U Angers). The latter group is already collaborating with the MINT unit for the formulation of an original tubulin peptide presenting an antitumor activity in vitro and in vivo. Due to this reorganisation, the scientific project will be then refocused on development of new formulations adapted to get through tissue barriers (either endothelial or epithelial).

Global assessment of the unit

The MINT unit has a strong expertise in the formulation of original lipid nanocapsules and microspheres. This multidisciplinary team is well recognized by the national and international community. Its research activities have led to the publication of an impressive number of original international articles during the present contract (close to 200) regarding the number of permanent staff in the unit. Most of the journals can be considered as good or even excellent (mean IF of 4.92, more than 80% of the papers are published in journals with IF > 3). The research activities of the unit have also led to 6 patents and the creation of a spin-off (Carlina technology). The unit is well funded through charities, industries and national or European projects. The research proposed for the next contract is sound and based on previous innovations. However, due to the restructuration of the unit, the biological applications for the new formulations look quite broad or non-sufficiently focused.

Strengths and opportunities in the context

The multidisciplinarity of the staff members is probably a strength of the MINT unit. This allows addressing the projects from a fundamental to an applied point of view. The unit will benefit from the local technical support of the Federative Research Structure (SFR) and the facilities of the Faculty of Pharmacy to get access to important technical platforms in the same building (e.g. animal housing, microscopy and imaging platform, cellular analysis, radiobiology). The unit has developed a good European collaborative network and good contractual links with the pharma industry. The financial support from the region and the industry is relatively high. The reorganisation of the unit with the venue of the two groups from the University of Angers should reinforce the biological expertise of the unit and provide the opportunity to develop new formulation strategies for an original and potent powerful tool for cancer treatment, the peptide NFL-TBS.40-63. To date, the unit had an excellent recruitment of PhD students.

Weaknesses and threats in the context

The important turnover of the permanent people may affect the dynamics of the unit and slow down its research activities. In 2010, 13 people arrived in the unit, and in the next contract 5 other people, including pharmacologists and biologists, will join the team, while 7 plan to move to the "Centre de Recherche en Cancérologie Nantes Angers". This represents an important fraction of the permanent staff. Recruitment of researchers or groups working on preclinical validation could reinforce the visibility and valorisation of the work.

As mentioned in the report, an increased number of research topics is not desirable given the relatively small number of permanent researchers. More particularly, the proposed research axis 2 of the project is extensive and could lead to the dispersion of the strengths.

Recommendations

The unit should try to recruit new researchers in order to counterbalance the staff reduction expected for the next contract. Moreover, it should be attentive to the integration of the newcomers and of their research activities to its global scientific strategy. The label by both INSERM and CNRS is important for researchers from these institutes. The development of new strategies to form nano- and micro-particles and the diffusion of nano-objects in hydrogels fit with the themes of the Section 11 and CID 54 of the CNRS. It is also vital for the future development of the unit and for maintaining the fruitful contacts with the pharma industry to preserve the QbD approach currently used for the conception of the pharmaceutical vectors.