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## Highlight CERIMED Newsletter N°4 December 2008

### EDITORIAL

Since the third CERIMED Newsletter (July 2008), significant progress have been made :

- the technical description of the CERIMED building has been completed. This was a difficult task because of the technical complexity of the building which is going to host a radiopharmaceutical laboratory with two cyclotrons, an animal farm, preclinical and clinical imaging platforms with cutting edge equipment, and several technical laboratories. This programming task was achieved thanks efficient discussions between Yves Dubois and Philippe Frère (company Couzane), Thierry Barontini, Christine Blanc, Laure Dumoulin and Elisabeth Goig (Université de la Méditerranée) and the CERIMED project team (Jean-Michel Bartoli, Eric Guedj, Benjamin Guillet, Isabelle Halgand, Paul Lecoq, Christian Morel, Olivier Mundler, Charles Oliver, Pascale Pisano and Vincent Vidal). Invitations to tender will be launched soon for the selection of an architect-civil engineering enterprise tandem.

- The company Advanced Accelerator Applications (AAA) s.a. has been selected in July 2008 by a jury nominated by the President of the Université de la Méditerranée. AAA will act as a private company hosted in the CERIMED building for the production and sale of radiotracers to hospitals in France and abroad. AAA will become as well as a partner of CERIMED for research and development on radiopharmaceuticals. The jury, acting under the direction of C. Oliver, was composed of administrative (Jacqueline Gautry, Michèle Lamarche and Damien Verhaeghe), technical (E. Goig) and scientific (P. Lecoq, C. Morel, O. Mundler and P. Pisano) persons.

- Work is in progress to define an institutional framework for CERIMED that will progressively evolve from an Association "Loi 1901" for the prefiguration of the CERIMED project towards a comprehensive European framework. The Université de la Méditerranée has considered the constitution of a Scientific Interest Group or GIS (Groupement d'Intérêt Scientifique) to be a satisfactory transient solution. A draft of a convention between several potential institutional partners is now under discussion for the constitution of this GIS.

- Within the Axe VI "Research in Technology" of the "Canceropôle PACA (Provence Alpes Côte d'Azur)", a meeting with the group of Medical Imaging of the "Canceropôle CLARA (Lyon Auvergne Rhône-Alpes)" has been held on December, 2<sup>nd</sup> 2008 in Lyon. Cooperation between physicians and physicists from both regions will be fruitful for the development of new imaging techniques and protocols that are targeting cancer.

- Following in particular the recommendations of the brainstorming workshop in Saint-Maximin in April 2008, the CERIMED project is entering now a new phase with the detailed description of the CERIMED building and its equipments, the definition of an institutional framework for CERIMED, and the launch of a number of CERIMED projects (instrumentation, radiopharmacy, clinical and preclinical validation, education, technology transfer). A growing number of people are

directly involved in these tasks and we would like to thank them all for their excellent work.

## **EXECUTIVE SUMMARY OF THE BRAINSTORMING WORKSHOP ON CERIMED – SAINT-MAXIMIN, APRIL, 24-25 2008**

A short reminder of the project status has been presented by C. Oliver. As an open centre for translational research in medical imaging, with a strong emphasis on education and training, CERIMED will have to promote and strengthen networking of competence at the European level, from fundamental research, detector developments, imaging probes and radiotracers, to preclinical and clinical research. Besides proactive networking activities, it will offer a unique infrastructure in the heart of the University Hospital of Marseilles opened to European scientists and industries involved in medical imaging research and development activities.

Thereafter, the participants (50 persons) were divided into two parallel groups :

- The strategic positioning of CERIMED at the academic-industrial interface in the future medical imaging landscape (Chair : Prof. David Townsend, University of Tennessee Medical Center).
- The European dimension of CERIMED : Why and how ? (Chair : Dr Robert Aymar, CERN General Director).

As a result of the lively discussions in the two working groups, a list of recommendations has been made along the following lines :

- 1) Improve and better target the communication on CERIMED and make its strategy more visible as an open centre with appropriate state-of-the-art infrastructure for interdisciplinary actions at the interface Technology-Health-Industry.
- 2) Develop networking activities that will include a strong French core and a number of European institutions acting as partners in all fields of CERIMED (technology, preclinical and clinical studies, education and training, industrial transfer).
- 3) Improve the CERIMED structuring with :
  - A legal structure under the French law, with the possibility to evolve towards an European institutional framework.
  - Increase CERIMED staff with competences for the preparation of European and industrial partnerships.

## **AAA : A PRIVILEGED CERIMED PARTNER**

The company AAA has been created in 2002 as a spin-off of the European Organization for Nuclear Research (CERN) with a patent on a technology allowing highly efficient radioisotope production. Today, A.A.A. is a European leader in the production of PET radiopharmaceuticals and is developing innovative products and technologies in the field of nuclear medicine.

Besides the [18-F] FDG (fluoro-deoxy-glucose) GLUSCANA®, AAA is committed to developing a large number of PET tracers. AAA is presently operating in France (Saint-Genis-Pouilly, Béthune, Troyes) and in Italy (Ivrea, Venafro). A new centre is under construction in Spain (Zaragoza).

Every AAA laboratory follows the Good Manufacturing Practice (GMP) rules for the production of radiopharmaceuticals that are initially developed for research purposes, before being registered as pharmaceuticals products.

An agreement between AAA and the Université de la Méditerranée is currently under preparation. This agreement defines the conditions of the partnership for research and development of new radiopharmaceuticals, as well as for the commercial exploitation products.

## **SIGNATURE OF A CONVENTION BETWEEN THE UNIVERSITE DE LA MEDITERRANEE AND INRS (QUEBEC)**

On July, 4<sup>th</sup> 2008, following the celebration of the 400<sup>th</sup> anniversary of the creation of state of Quebec, the CERIMED Coordinator Charles Oliver and Pierre Lapointe, General Director of INRS (Institut National de la Recherche Scientifique) of Quebec have signed an important protocol of cooperation between the Université de la Méditerranée and INRS in presence of François Fillon, Prime Minister of France, and Jean Charrest, Prime Minister of Quebec. The CERIMED project is included in this convention which allows both institutions to cooperating for their mutual benefits in the fields of optics and photonics applied to biomedical research and medicine within the project CIEL-ASUR.

The purpose of the project CIEL-ASUR (Composants pour l'Institut de l'Extrême Lumière et Applications des Sources Ultra-Rapides) is to build an interdisciplinary original platform that will be implementing a new ultra-fast, high power laser. Its potential will be investigated for stimulated X-ray production for medical imaging with high spatial and timing resolution, for ophthalmology and for isotope production. Space has been reserved to accommodating this equipment closely to the CERIMED building. The project is led by the laboratory LP3 (Lasers, Plasmas and Photonic Processes) directed by Marc Sentis and by the Energy, Materials and Telecommunications group of INRS directed by Jean-Claude Kieffer.

INRS is a network of four research centers located around of Quebec and Montreal, whose activities are oriented in sectors of strategic importance :

- Water, earth and environment ;
- Energy, materials and telecommunications ;
- Human, animal and environmental health (Institut Armand-Frappier) ;
- Urbanization, culture and society.

## **CERIMED AND THE ECOLE CENTRALE OF MARSEILLES**

- For the second consecutive year, a three ECTS (European Credits Transfer System) course on human anatomy and pathophysiology is being taught to third year students in engineering at the Ecole Centrale of Marseilles. Lectures include basics in anatomy, physiology and pathology of several human functions : endocrine, cardiovascular, respiratory, digestive, uro-genital and osteo-muscular. For each case, special reference is given to imaging applications. General information is also given in the field of medical imaging and about the organization of the health system and clinical research. The course on human anatomy and pathophysiology may be completed by training periods in the department of radiology and nuclear medicine.

- An overview of the field of medical imaging and of the CERIMED project has been given by Eric Guedj and Charles Oliver to the students in engineering at the Annual Meeting on Research and Development organized by the Ecole Centrale on November, 18<sup>th</sup> 2008.

## TECHNICAL NOTE ON THE CERIMED PILOT PROJECTS (3)

### ClearPEM SONIC

The early detection of breast cancer is becoming a priority in healthcare policy of an increasing number of countries. A large number of women (about one out of eight) will develop a breast cancer, which is the second leading cause of mortality from cancer. On the other hand, early detection of breast cancer leads to very high cure rate. In the end of the seventies, the introduction of X-ray mammography breast cancer screening every 18 to 28 months (depending on the country) offered an important advancement against breast cancer development. By permitting early detection of this illness, a reduction of the order of 29% in the mortality by breast cancer was achieved, according to the analysis of the first clinical data.

Morphologic methods, like conventional X-Ray mammography or echography show lesions, not cancers. Moreover breast cancer is very often characterized by low contrast structures in the domain of low energy X-rays, which leads to a low sensitivity. In particular, for the 40% of women having dense breasts X-rays mammography misses about 50% of cancers. This is particularly unfortunate if we consider that breast densification is often associated to estrogen treatment, which could be related to a significantly higher risk of breast cancer. Moreover the lack of specificity of these imaging methods leads to a high rate of false positive and to a large number of unnecessary biopsies.

The introduction of magnetic resonance techniques, in addition to the previous methods, may bring a better sensitivity, but apparently does not improve its specificity. With severe limitations in frequent benign pathologies, like fibroadenoma and fibrocystic disease, and with difficulties of interpretation in glands previously submitted to surgery, we may anticipate that the number of false positive will be substantially larger than with X-ray mammography uniquely.

CERIMED proposes an approach based on the ClearPEM<sup>®</sup>, a dedicated positron emission camera for mammography coupled with an advanced ultrasound device with echographic and elastographic measurement capabilities developed by the company Supersonic Imagine based in Aix-en-Provence. Images will benefit from the fusion of the information specific to each one of the modalities and will combine altogether a molecular, morphological and anatomical imaging information. An artistic view of the machine is shown on Fig. 1.



Fig. 1: Artistic view of the ClearPEM-Sonic (Courtesy J. Varela, LIP, Lisbon)

The ClearPEM<sup>®</sup> is a unique dual-head Positron Emission Mammography scanner using avalanche photodiode (APD)-based detector modules with the capability of measuring depth-of-interaction (DOI) with a resolution of 2 mm within very dense Cerium doped Lutetium-Yttrium oxy-orthosilicate scintillating crystals (LYSO :Ce). These specifications will make it possible for the detection of 3 mm breast lesions in less than 7 minutes exams, thanks to the image spatial resolution of 1.2 mm and to the high sensitivity of the detector device. The full system comprises 192 detector modules in a total of 6144 LYSO:Ce crystals and 384 32-pixel APD arrays arranged in two detector plates rotating around the breast encompassed with a cone applying minimum compression. This will improve the comfort of the patient who will be installed on a table in prone position with a hanging breast (Fig. 1). A first prototype of the ClearPEM<sup>®</sup> has been built by a Portuguese consortium in the framework of the Crystal Clear collaboration based at CERN. This system is now installed in the hospital of Porto for a first clinical evaluation. A second imaging system is under construction for the present project. An ultrasound scanner of the next generation capable of quantitatively mapping the elastic properties of the tissues will be installed under the table to complementing the functional information provided by the ClearPEM<sup>®</sup> with morphologic and structural information about the lesions.

ClearPEM-Sonic is a 1.3 M€ project, which has been labelled by the Pole of Competitiveness OPTITEC ("Pôle de Compétitivité Photonique, Systèmes Complexes d'Optique et d'Imagerie") of the region PACA (Provence-Alpes-Côte d'Azur). This international and multidisciplinary project groups the following partners, including two companies in France and Portugal :

1. The European Organization for Nuclear Research (CERN), an intergovernmental organization based in Geneva, Switzerland ;
2. The Vrije Universiteit Brussel (VUB), Brussels, Belgium ;
3. The Laboratório de Instrumentação e Física Experimental de Partículas (LIP), Lisbon, Portugal ;
4. The Université de la Méditerranée (Aix-Marseille II), Marseilles, France ;
5. Assistance-Publique – Hopitaux de Marseille (AP/HM), Marseilles, France ;
6. Institut Paoli – Calmettes (IPC), Marseilles, France ;
7. Laboratoire de Mécanique et d'Acoustique (LMA), CNRS, Marseilles, France ;
8. The Università degli studi di Milano-Biocc, Milano, Italy ;
9. The Universiteit Gent, Gent, Belgium ;
10. Supersonic Imagine, Aix-en-Provence, France ;
11. PETsys-Medical PET Imaging Systems S.A., Oeiras, Portugal.

The ClearPEM-Sonic is an essential tool for the future activity of CERIMED in Marseilles. The large international consortium, which is directly or indirectly (Crystal Clear collaboration) associated to this project represents eventually a first and important step towards the European deployment of CERIMED. Moreover, the development of public-private partnerships, as well as incentives for joint industrial ventures is fully consistent with the CERIMED industrial strategy.

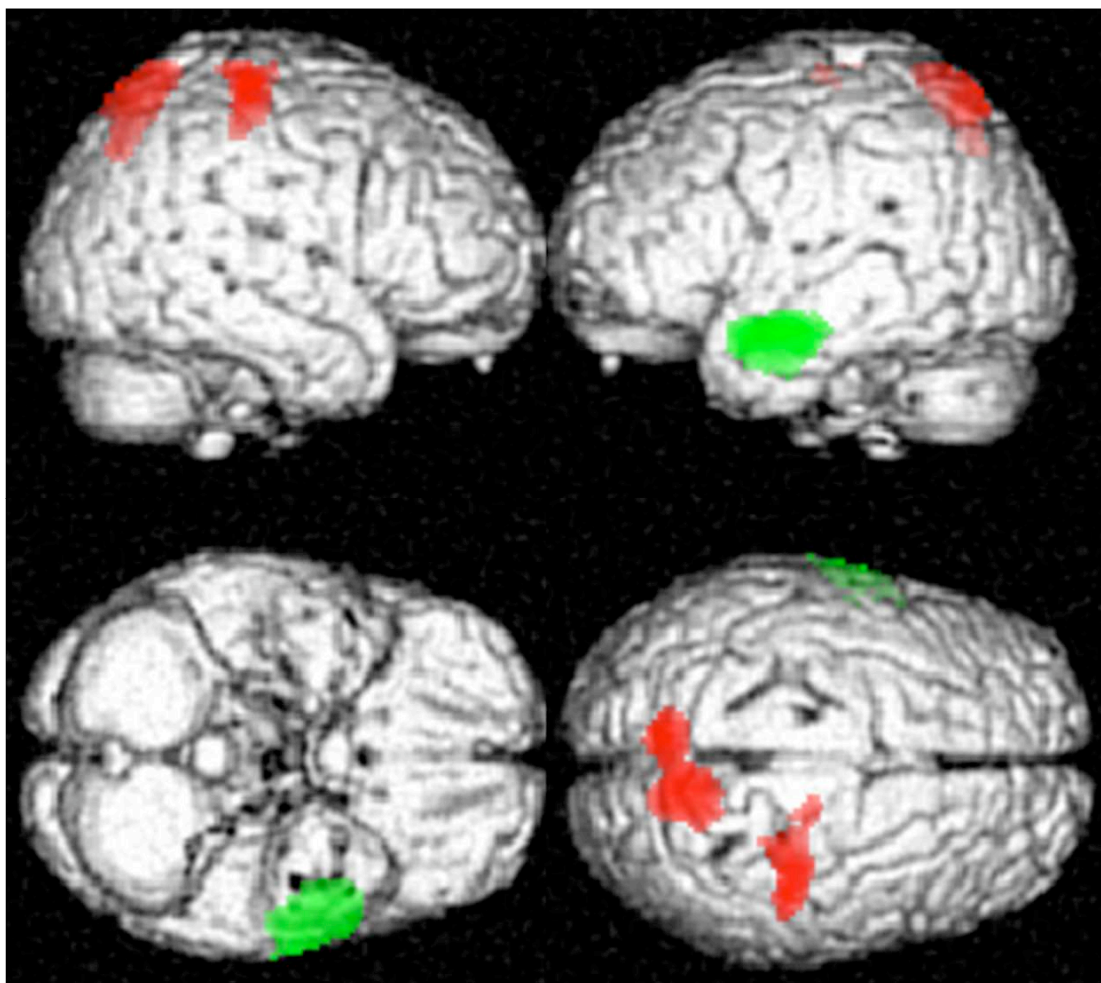
## **CLINICAL NOTE ON THE CERIMED PILOT PROJECTS (1)**

Five clinical studies have been approved so far by the technical committee of the Clinical Investigation Centre of Marseilles. Three of them are in oncology (two on

breast and one on thyroid gland) and two in neurology. Eric Guedj (Department of nuclear medicine, University Hospital Timone) is currently developing a research program on patients with fibromyalgia, which is a complex, chronic disease characterized by muscle pain and fatigue. Following the recent discovery by the same research group of functional abnormalities in the brain of patients with fibromyalgia, the aim of Eric Guedj is to modulate the brain activity of affected areas by repetitive Transcranial Magnetic Simulation (rTMS).

Whereas some authors are suggesting that this syndrome could be related to a mental disorder, this new study proposes another explanation, because brain functional abnormalities were found in brain regions involved in pain processing correlated with disability of patients. Interestingly enough, these abnormalities were independent from anxiety and depression status, providing further evidence for a genuine cerebral disease.

These findings have been published in the November issue of The Journal of Nuclear Medicine(\*).



This study shows hyperperfusions in parietal areas involved in sensory dimension of pain (*in red*) and hypoperfusions in anterior temporal areas known to be involved in affective dimension of pain (*in green*). These functional brain abnormalities were found in comparison to healthy subjects, and were correlated with disability independently of anxiety and depressive status.

(\*) : Guedj E, Cammilleri S, Niboyet J, Dupont P, Vidal E, Dropinsli JP, Mundler O. Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia. *Journal of Nuclear Medicine*. 2008 ;49:1798-803

## 5<sup>TH</sup> THEMATIC WORKSHOP ON STEM CELL IMAGING

Following the success of the breast imaging symposium organized in 2001 in Rome, the workshop on prostate imaging and the one on vascular imaging, the Istituto Superiore di Sanita and CERIMED have organized a new symposium, in collaboration with the French "Canceropôle PACA", the Universities Roma I and Roma II, the National Institute for Nuclear Physics (INFN) in Italy and Jefferson Lab in the USA :

"Stem cells research : the role of imaging techniques".

This event took place in Marseilles (Hôpital de la Timone) on December, 8-9<sup>th</sup> 2008.

A report on this event will be published in the next CERIMED Newsletter.

### CONGRATULATIONS TO PAUL LECOQ !

Paul Lecoq has recently been elected as a member of European Academy of Sciences (EAS – <http://www.eurasc.org>). This Academy, created in 1999, is composed of international researchers and teachers whose quality of works and their application to the social and economical development is acknowledged all over the world.

P. Lecoq has received is diploma as engineer in physics instrumentation at the Ecole Polytechnique de Grenoble in 1972, under the direction of Nobel Laureate Louis Néel. After two years of work at the Nuclear Physics laboratory of the University of Montreal, Canada, he got his PhD in Nuclear Physics in 1974. Since then he has been working at CERN in 5 major international experiments on particle physics, two of them led by the Nobel Laureates Samuel Ting and Carlo Rubbia. His action on detector instrumentation, and particularly on heavy inorganic scintillator materials has received a strong support from Georges Charpak. Member of a number of advisory committees and of international societies, he is the promoter of CERIMED since 2002 and its Technical Director.

**Charles OLIVER , project leader**  
**Paul LECOQ , technical director**  
**Olivier MUNDLER, medical director**

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