

## Highlight CERIMED Newsletter N°5 July 2009

### EDITORIAL

Since the last Newsletter dated on December 2008, the CERIMED project has reached important milestones in line with its original ambition to become an open campus at the European level for the academic and industrial actors of medical and molecular imaging and to provide this pluridisciplinary community with an environment for translational research and development aiming at a fast transfer to the patient.

The design of the infrastructure has been refined with the objectives to improving the integration of CERIMED on the campus of the Timone School of Medicine and the communication with the hospital. On top of the constraints involved by the installation of different technical laboratories and a large assembly hall linked with all the CERIMED sections, a particular attention has been paid to fulfil the complex safety, veterinary, clinical and ethical rules (use of radioactive products, housing of rodents and big animals, accommodation of patients). Moreover, the future location of CIEL ASUR (high power femtosecond laser, LP3, UMR 6182 in collaboration with INRS, Montreal) has been studied next to the preclinical imaging section of CERIMED. This will provide CERIMED with a unique installation for the development of ultra-small X-ray sources, as well as for high precision dynamical studies and advance technologies for the production of radiotracers.

The *Université de la Méditerranée* has subcontracted the *Maîtrise d'Ouvrage* (i.e. the organization, scheduling and follow-up of the construction) to the private group *Marseille Innovation* under a strict budget control managed by the university.

The schedule for the funding operations of the CERIMED infrastructure by the local institutions (Regional Council, Department Council, City of Marseilles) and by the European Union is now well defined and under control. Last but not least, the agenda for purchasing equipments is under discussion.

In addition to these administrative actions, the following scientific activities of CERIMED are ongoing on:

- organization of thematic workshops;
- validation of clinical studies in the fields of neurosciences, cancer and cardiology;
- R&D on the technical projects tomXgam (development of the ClearPET/XPAD small animal hybrid PET/CT scanner) and ClearPEM Sonic (dual modality breast imaging that will be delivered to the *Hôpital Nord* in Marseilles in December 2009) developed by a large European consortium;
- preparation of two new European collaborative projects involving prestigious academic and industrial partners.

## **AGREEMENT BETWEEN THE ADVANCED ACCELERATOR APPLICATIONS (AAA) COMPANY AND THE UNIVERSITE DE LA MEDITERRANEE**

The contract agreement has been signed at the university headquarters on June, the 25<sup>th</sup> 2009 by Dr. Stefano Buono, President of Advanced Accelerator Applications (AAA) and Pr. Yvon Berland (President of the *Université de la Méditerranée*).

The company AAA is responsible for the procurement, installation and running of 3 radiopharmaceutical laboratories and two cyclotrons in the CERIMED building, one for commercial use and the other one for exploitation within a research partnership between CERIMED and AAA.

AAA is a European leader in the production of PET radiopharmaceuticals. It is developing innovative products and technology in the field of nuclear medicine. The company has been launched in 2002 and is considered as a CERN spin-off. It is now operating five production sites: Saint-Genis Pouilly (Ain in France) since 2002, Venefro (between Rome and Naples in Italy) since 2006, Ivrea (Piemonte in Italy) since 2007, Béthune Hospital (Northern part of France) since 2009, and Aube's Technopark (Troyes in France) since 2009 too.

AAA is quite active in research and development as assessed by:

- the production of new original research PET tracers with the authorization to validate these tracers in the framework of preclinical and clinical studies;
- the development of medical devices for nuclear medicine;
- the development of synthesis modules and processes that will result in new available products;
- its participation in the development of the *Bioindustry Park* of Canavese in Italy, which involves a new company named *EØoran* whose aim it to provide multi-imaging preclinical and clinical solutions in the framework of a European centre for preclinical imaging.

Hence, the facility operated by AAA and CERIMED within a School of Medicine Campus will undoubtedly provide an invaluable environment for the development and validation of new and specific markers for various pathologies.

## **THE PILOT PROJECTS OF CERIMED**

In addition to the 3 technical pilot projects (tomXgam, ClearPEM-Sonic and POCASI) described in previous newsletters, and to two educational projects, nine CERIMED clinical research projects have been validated by the Technical Committee of the Clinical Investigation Centre of Marseilles (CIC) and have been included into the Clinical unit of CERIMED since July 2008 :

- four in neurosciences:
  - Set up of a normative neuroimaging database for healthy subjects.
  - Repeated transcranial magnetic stimulation of motor cortex in fibromyalgia: double-blind randomized prospective study for the evaluation of the analgesic efficacy and its metabolic correlation with 18-FDG PET.

- Brain metabolism study during spontaneous crisis of vascular algia of the face.
  - Sporadic Alzheimer disease with early and late onset: study of the variation of the clinical, biological and radiological phenotypes with regards to the age of the symptom onsets.
- four in cancer :
    - Evaluation of thyroid nodules by elastography coupled to echography (this study has been completed).
    - Optimization of the acoustic specifications of echographic and elastographic scanning modes of a prototype US scanner for breast imaging.
    - Assessment of the clinical value of SuperSonic shear wave elastography in the US evaluation of breast lesions.
    - Translational studies on the expression of glucose transporters (GLUT1 and GLUT3) in human glioblastomas: correlation with metabolic imaging (PET-CT) and prognosis impact.
  - one in cardiology :
    - Evaluation of heart CT with dipyridamole injection in the diagnosis of myocardial ischemia: comparison with scintigraphy as the gold standard.

### **Evaluation of thyroid nodules by elastography (short description )**

The research project on the evaluation of thyroid nodules by elastography is the first CERIMED project that has already been completed. The results have been presented at the Endocrine Society meeting in Washington (June 10-13<sup>th</sup> 2009) and will be submitted for publication in Clinical Endocrinology:

« ShearWave™ Elastography (SWE): a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules ».

⇒ This is the first clinical project of CERIMED. This cooperative project has been set up in the frame of a collaboration between the Departments of Endocrine Surgery, Endocrinology and Metabolic Diseases, Radiology (Timone Hospital), Public Health Laboratory (Medical School), and the SuperSonic Imagine Company based in Aix-en-Provence. The study was supported by a grant from *Assistance Publique/Hôpitaux de Marseille* and the main investigator was Dr. Frédéric Sebag, endocrine surgeon.

⇒ Background:

→ Thyroid nodules are very common clinical findings with an estimated prevalence ranging between 5.3% in women and 0.8% in men in the Whickham survey. This prevalence increases up to 40-50% with ultrasound examination of the thyroid gland, the palpation of the follicular adenoma, cysts, thyroiditis. 5 to 15% of them being malignant.

→ Thyroid ultrasound is used as a first-line procedure to help differentiating benign and malignant nodules. Several US features have been associated with malignancy. However these features are poorly predictive when taken singly. The combination of their features increases the specificity, but the sensitivity becomes low. Cytological

examination of material collected by fine needle aspiration (FNA) is now the best test for differentiating malignant from benign thyroid lesions with diagnostically useful results in about 70 percent of solitary nodules. However, there are some limitations to the use of FNA: lack of sufficient material for cytological examinations, inconclusive results or difficulty in FNA if several nodules are present in the thyroid gland.

→ During the last few years, a new diagnostic strategy has emerged, elastography that uses ultrasound to assess tissues elasticity. A technique that requires external compression by the user has shown great potential for the diagnosis of cancer in single thyroid nodules. ShearWave™ Elastography (SWE) is a new technique, originally developed by SuperSonic Imagine. Based on automatic generation and analysis of transient shear waves, this mode has the advantage of being quantitative, real time and user independent.

The aim of this study was to assess the efficiency of SWE in predicting malignancy and to compare SWE with classical US characteristics.

⇒ Patients and methods:

Ninety-three patients (61 with solitary nodules and 32 with multiple nodules) and 39 control patients were included in this study. The predictive value of SWE has been assessed by the correlation between nodules' elasticity, conventional US parameters and histological examination (on surgical specimens in 71 cases and on FNA cytology in 14 cases). Scores have been constructed with echographic parameters: absence of a halo, central vascularization, hypoechogenicity and microcalcifications (Score 1) and with echographic parameters plus elasticity index (Score 2). Statistical analysis (uni and multivariate analysis, ROC curves) was used.

⇒ Results:

One hundred and forty-six nodules were analyzed in 93 patients. Twenty-nine nodules were malignant (19.9%) with papillary (n=20), follicular (n=5), undifferentiated (n=2), medullary (n=1) and anaplastic (n=1) variants. The mean elasticity index was 150 Kpa ± 95 (30-356) in malignant nodules vs. 36 KPa ± 30 (0-200) in benign nodules (p<0.001, Student's T test).

For a positive predictive value > 90%, the characteristics of the Score 1 were: sensitivity = 44.4% and specificity = 99% and of the Score 2 : sensitivity = 74% and specificity = 98%.

⇒ Conclusion:

SWE is a powerful technology in the evaluation of thyroid nodules, which improves the sensitivity of conventional US. This technique could be helpful especially in conditions where FNA is difficult (multiple nodules) or less reliable (nodules of less than 15 mm). Further multicentric studies are necessary for confirmation of these results and for evaluation in various thyroid cancer types.

## **JOINT MEETINGS BETWEEN CANCERPOLES LYON-AUVERGNE-RHONE-ALPES (CLARA) AND PROVENCE-ALPES-COTE D'AZUR (PACA)**

Medical imaging is well identified among the activities of both *Canceropôles* :

- It is the central topic of the axis 1 of the *Canceropôle CLARA*.

- In the *Canceropôle PACA*, CERIMED is included in its 6<sup>th</sup> axis entitled "Research in Technology". The chairmen of this axis are Jean-Pierre Gérard (for radiotherapy) and Olivier Mundler (for medical imaging).

Three meetings have been organized in Lyon (December, the 2<sup>nd</sup> 2008), Marseilles (February, the 3<sup>rd</sup> 2009) and Archamps (March, the 24<sup>th</sup> 2009). The headings of the meetings are summarized below.

- 1 – Presentation of the activities of all the partners from Lyon, Clermont-Ferrand, Grenoble, Nice and Marseilles.
- 2 – Identification of possible joint collaborative programs to be raised in the domains of education/training and clinical and pre-clinical investigations.
- 3 – Development of new medical imaging approaches for the localization of cancer lesions before and during surgery. Pr. John Prior from the Nuclear Medicine Department of the University Hospital of Lausanne (Switzerland) is also actively involved in these projects.

## **THEMATIC WORKSHOPS OF CERIMED**

Following the success of the first 4 international thematic workshops on PET Data Acquisition systems (Marseilles CPPM, 14-15 September, 2006), Cardiovascular Imaging (Rome ISS, 13-14 November, 2006), Breast Imaging (Marseilles Timone, 25 January, 2007) and CERIMED Brainstorming (Saint Maximin, 24-25 April, 2008), CERIMED and the *Istituto Superiore di Sanita* (ISS) in Italy have organized a 5<sup>th</sup> thematic workshop on stem cells research: the role of imaging techniques.

### **The 5<sup>th</sup> thematic workshop on stem cell imaging: ISS/CERIMED Marseilles – Dec, 8-9 2009**

This workshop gathered 50 participants from several European countries as well as from USA, who have actively discussed in Marseilles Timone on Dec, 8-9 2008 about the crucial role but also the challenges of in-vivo imaging of stem cells. The main focus of this very important and timely meeting was (1) understanding the status of cell tracking technologies, (2) definition of the required imaging performance specifications for the preclinical and clinically relevant imaging tasks, (3) evaluation of the available or potential imaging technologies applicable to these imaging tasks, and (4) definition of the necessary directed R&D effort towards the goal of better stem cell localization and monitoring. The workshop has been organized by Dr. Franco Garibaldi (ISS) and Dr. Paul Lecoq (CERN).

With the emergence of stem-cell based treatments in cardiology, oncology, immunology, neurology, transplantation, there is an increased demand for in-vivo tracking of a small number of cells.

As an example cell therapy for cardiac repair has emerged as one of the most exciting and promising developments in cardiovascular medicine. Evidence from experimental and clinical studies is increasing confidence that this innovative treatment may influence clinical practice in the future. But before stem cell-mediated cardiomyoplasty can be applied in the clinic, basic research must be performed using animal models to address critical issues: do grafted cells survive in sufficient numbers to be biologically meaningful ? can grafted cells differentiate into cardiomyocytes in response to local stimuli ? do grafted cells contribute to the improvement of contractile function in addition to the improvement of global function ?

Similar questions arise from other possible applications of stem cells, such as brain diseases (stroke, Parkinson, Alzheimer). Moreover, recent research showed the role of tumour stem cells in carcinogenesis and metastasis proliferation. Open questions remain with regard to the basic mechanisms of stem cell therapy and emphasize the need for specific techniques to visualize the effects of stem cell therapy in-vivo. This concerns essentially biological vectors, tracers, new detectors, and new imaging modalities.

The imaging modalities known today for having the highest sensitivity are based on optical fluorescence or positron emission tomography (PET).

Unfortunately, the presently used standard clinical nuclear medicine imagers for single gamma imaging (gamma cameras) and for positron imaging (PET scanners) are not optimized for this task. These generic large instruments and their associated poor spatial resolution and sensitivity are inferior to what can be potentially achievable with optimized dedicated imagers and procedures. A similar situation concerns other imaging modalities, such as MRI.

During these two days extensive discussions took place about high resolution, high sensitivity detectors as well as novel multimodal approaches to be developed, aiming at non-invasive, repetitive visualization of cells in vivo. There is a need in particular for advanced multimodality imaging procedures, combining the high spatial resolution of some morphological techniques (MRI, CT) and the high sensitivity of nuclear imaging modalities. Optical techniques are also likely to play an important role in preclinical research. Such imaging approaches would refine the understanding of therapeutic mechanisms in basic experimental studies.

It is precisely in the mission of CERIMED to set the grounds for the development of future imaging technologies, aiming at better in-vivo visualization and quantification of cellular and molecular processes. This international workshop has greatly contributed to better identify the challenges of imaging and tracking a few stem cells in a human being, which counts about 100'000 billions of cells.

### **The 6<sup>th</sup> thematic workshop on GPU computing: GDR MI2B/CERIMED Obernai – May, 28-29 2009**

A workshop on the development of parallel computing applications on Graphics Processing Units (GPUs) for molecular imaging gathered about thirty participants coming from all over France in Obernai, near Strasbourg, on May, 28-29 2009. It was sponsored by CERIMED and by the IN2P3 French Group for Research (GDR) "Modelling and Instrumentation for Biomedical Imaging" (MI2B) and organized by David Brasse (*Institut Pluridisciplinaire Hubert Curien, UMR 7178, Strasbourg*) and Christian Morel (*Centre de Physique des Particules de Marseille - CPPM*). It allowed to discuss the extraordinary potential of GPU architectures to shorten drastically the computing time necessary for the reconstruction of slices in computed tomography. The participation of specialists in medical imaging and computed simulation, of representatives from the two main GPU manufacturers NVIDIA and AMD, and of integration companies such as digisens or SEGAMI, made it possible to initiating fruitful contacts between the various actors of this emerging technology.

The workshop started with a survey of the challenges that medical imaging has to face, particularly with regards to dynamic image reconstruction or 4D reconstruction, and to Monte Carlo simulations that must be customized to the patient case for improving the quality of diagnostic information transmitted to the clinicians. The manufacturers and the integrators delivered their vision of a rapidly evolving GPU environment for massive parallel computing, which will soon achieve better programming frameworks that will be more user friendly. Last but not least, attendees have presented their porting of reconstruction algorithms on GPUs for Cone Beam Computed Tomography (CBCT), for nuclear medicine

emission tomography, and for real-time manipulation and visualization of 3D medical images.

The workshop ended with a round table centered on the future of this new approach for high performance computing. Is it going to stagger like it was the case for the Transputer based parallel computing industry that has been caught up during the 90s by the improvement of the performance and speed of CPU used in personal computers ? or is it going to grant access on the mid term to a cost effective and extraordinary powerful computing that has been reserved so far for the supercomputers of civil and military research organisms ? Let's bet that the development of free software tools such as the OpenCL programming environment that is oriented towards the portability of applications developed for GPUs, as well as the mass market driving force constituted by the videogame industry that is supporting the development of GPUs of high performance and at affordable prices, are promising together a bright future for this novel high performance computing approach, which was still in its infancy just a few months ago.

### **The 7<sup>th</sup> thematic workshop – Marseilles – June, the 26<sup>th</sup> 2009**

The 7<sup>th</sup> thematic workshop on "Optics in Medical Imaging" has been organized on June, 26<sup>th</sup>, by CERIMED, POPSUD, the *Canceropôle PACA* and EuroBioMed.

The aim of this workshop was to sensitize the photonic industry, and in particular the large number of SMEs associated to the cluster *OPTITEC Pôle de Compétitivité* to the rapidly increasing impact of photonics in optical and non-optical medical imaging modalities.

### **The 8<sup>th</sup> thematic workshop**

The 8<sup>th</sup> thematic workshop on "Advanced Molecular Intraoperative Probes Assisting Surgical Intervention in Cancer Treatment" will be co-organized by the Italian *Istituto Superiore di Sanita* (ISS) and CERIMED on Sep, 5-6 2009 in Baia delle Zagare in Italy (<http://www.hotelbaiadellezagare.it>).

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## **COMMUNICATIONS AND PUBLICATIONS OF CERIMED**

1 – A poster entitled "Shear Wave elastography<sup>TM</sup>: a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules" has been presented at the 91<sup>th</sup> annual meeting of the Endocrine Society in Washington DC, June, 10-13 2009 by F. Sebag.

2 – Pr. Pascale Pisano (UMR-S 608) has given a talk entitled "Stem cell therapies for ischemic diseases. Where do the cells go ?" at the workshop "Imaging from Molecules to Man: Challenges Toward Multi-Scales Approaches" which took place at the *Istituto Superiore di Sanita*, Roma – Italy on May, 21-22 2009.

3- Paul Lecoq (CERN) gave the opening talk of the SCINT09 conference on inorganic scintillators and their applications, Jeju Island (South Korea), June, 8-12 2009: "Molecular Imaging Challenges with PET and SPECT".

## **CONGRATULATIONS TO DAVID TOWNSEND**

Pr. David W. Townsend is going to receive the title of Doctor Honoris Causa of the *Université de la Méditerranée* on Nov, the 26<sup>th</sup> 2009 in Marseilles.

D. Townsend was born in 1945 in England. He obtained his bachelor of Sciences in Physics (University of Bristol, 1966) and his Ph.D. in Experimental High Energy Physics (University of London, 1971). Then, D. Townsend devoted his research to medical imaging. He is a pioneer in the development of PET imaging and made decisive contributions to the development of 3D PET (1978) and of combined PET/CT (1999, invention of the year, Time Magazine 2000).

D. Townsend has been distinguished Clinical Scientist of the year by AMI and received in 2008 the Medal of Pioneers in Medical Imaging from the Institute for Electrical and Electronic Engineers (IEEE).

D. Townsend conducted his research at CERN, at the University of Geneva (Switzerland) at the Hammersmith Hospital in London. He then became Professor at the University of Pittsburgh School of Medicine. Since 2003, he is Professor at the University of Tennessee School of Medicine, Knoxville (USA).

D. Townsend has always been very active in the CERIMED project since the early days. He is a member of the CERIMED committee and he acted as the chairman of the working group on the European deployment of CERIMED at the CERIMED Brainstorming Workshop held in Saint-Maximin in April 2008.

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