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European Centre for Research on Medical Imaging

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Contributions

This document was prepared by an ad-hoc provisional structure aiming at creating a European Research Centre in Medical Imaging, Cerimed. It was supervised by an executive committee and by a project committee, who jointly coordinated their action under the leadership of Professor Charles Oliver ("Université de la Méditerranée"), Cerimed's appointed project leader. Distinguished experts from abroad (Europe and out of Europe) are attending these committees, and we thank them here for the international dimension they have procured to this project.

A writing committee was set up under the supervision of Patrick Le Du (CEA-DAPNIA, Saclay), with: Charles Oliver, project leader ("Université de la Méditerranée"), Paul Lecoq, technical director (CERN), Oliver Mundler, medical director ("Université de la Méditerranée"), Christian Morel (CPPM) and Thierry Pourcher (CEA-TIRO, Nice).

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Executive Summary

Definition

This project for the creation of a European Research Centre in Medical Imaging (Cerimed) is supported by the "Université de la Méditerranée" in Marseille (France), in partnership with many national and European laboratories, academic institutions and industry.

The goal of Cerimed is to provide an environment of synergistic exchanges between the different scientific disciplines involved in medical imaging and industry. The objective is to create, within Europe, a center with the necessary expertise and infrastructure to support an ambitious research and development program in medical imaging and prepare future generations of medical imaging systems, a decisive contribution towards solving the great public health issues of our time.

Goals

The mission of the Cerimed centre is to establish European leadership in medical imaging by creating and amplifying the synergy between the groups and organisations involved at both the institutional and industrial level. This centre with a European perspective, is based on six objectives:

- Technical development in the field of imaging
- Transfer to clinical applications (diagnosis, therapeutic follow-up and clinical research)
- Transfer to pre-clinical research (studies on animals)
- Development and validation of new radiotracers
- Education, training and diffusion of knowledge
- Industry.

Cerimed is especially suited to address the following issues:

- meet the rapidly increasing demands of clinicians and biologists for new imaging techniques for humans and respond to the molecular imaging needs for pre-clinical studies on animals;
- create a community of interests in this field for physicians, biologists, physicists and industry representatives all over Europe;
- help medical imaging to benefit from recent impressive technological advances in the fields of particles detectors, of information technology and of micro- and nano-technology, through a multi-disciplinary approach;
- develop a common culture between the various disciplines involved (physics, biology and medicine) and industry, along with an education and training mission;
- ensure efficient technology transfer to industry due to numerous research partnerships and a fruitful exchange between academic and industrial institutions;
- establish a European leadership in the field of molecular imaging by providing an organising structure that combines the numerous skills which already exist in France and in Europe and are at present strongly attracted to the environment of the United States.

Technical facilities

To reach the stated objectives, Cerimed will establish on-site an infrastructure that offers the possibilities to:

- build advanced prototypes based on innovative and diverse technologies;
- validate these prototypes through animal and clinical studies.

To simultaneously fulfil its mission in terms of education and training and work in close partnership with industry, focusing on validation of technology, Cerimed must be established near a teaching hospital, large academic institutions (universities, schools of engineering) and a scientific industrial park.

Therefore the proposed site is the teaching hospital La Timone, which works in close collaboration with the technological centre of Chateau-Gombert in Marseille, France. This choice is justified by the attractiveness of Marseille at the European level, and by the high quality of many medical and research institutions and large academic and industrial organisations in the Provence-Alpes-Côte d'Azur region, and in the nearby Rhône Alpes region.

Building comprising of a total surface area of 2500 m^2 for an estimated cost of 7.5 M€ will be required to assemble all the equipment and infrastructure within a single environment where physicians, physicists, engineers, biologists and industry can closely interact.

All the technical equipment and infrastructure, including 1—and, in a second phase, 2—cyclotron should cost 12 M€ (15 M€ with the second cyclotron).

Cerimed will initially require 35 permanent staff—15 engineers/technicians, 15 researchers (physicists, physicians and biologists) and 5 administrative staff—and will host about ten students. In the second phase, the number of researchers and students will be progressively doubled.

Operating costs, including salaries, will amount to 9 M€/year in the first phase and 15.5 M€/year in the second phase.

Institutional structure of the project

A special supra-institutional status is desired, so that Cerimed can:

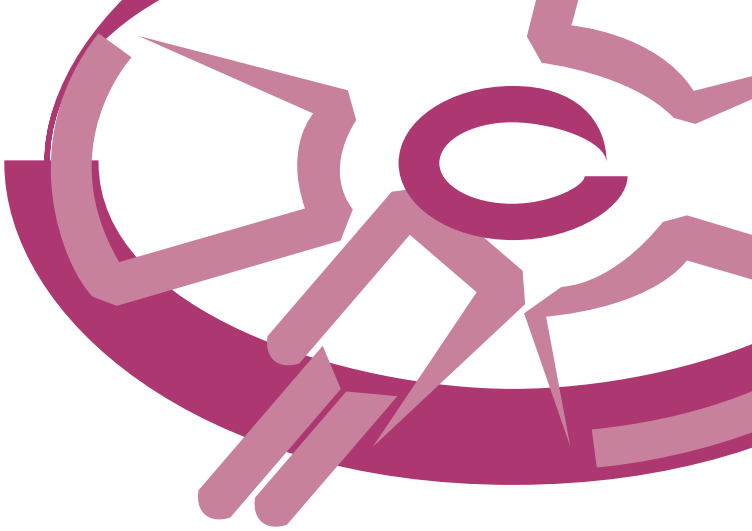
- manage the European dimension of the programme with a level of supervisionfrom the relevant ministries;
- co-ordinate as flexibly and independently as possible the various institutional and private partners at the European level.

Cerimed can already rely on a number of existing European networks in the field of instrumentation—the Crystal Clear, SIAM, CIMA and EuroMedIm collaborations, initiated by CERN or by the high energy physics community, GDR MI2B at the IN2P3/CNRS and at the DAPNIA/CEA—, biology—"génopôle" network (french coordination of research on genetic studies) —and medicine—"cancéropôle" network (french coordination on fighting cancer), European Association of Nuclear Medicine (EANM), Organisation of European Cancer Institutes (OECI). Cerimed will provide these networks with a place to interact at the European scale, and with logistical support and critical mass (as the large European research organisations dedicated to fundamental research—CERN, ESRF. . .—already do), making it possible to develop an industrial network which is still very limited in this field in Europe.

It is suggested that Cerimed's partners should be assembled as a European Scientific Interest Group (GIS) with a convention defining how each partner should participate, how intellectual and transferable property should be managed and how researchers and students should be hosted.

The financial structure will reflect the centre's goals: favouring technology transfer and coordinating research, innovation and industry. A Public-Private Foundation, or its European counterpart, a European Cooperative Society, could provide such a framework.

Contents



Introduction

The basis for medical imaging dates back over 100 years since Wilhelm Roentgen first took a picture of the bones of his wife's hand after exposing it to X-rays. Since then, spectacular developments have radically modified the course of medicine on a number of occasions. Since Roentgen's discovery—which was made accidentally—other diagnostic techniques that image living tissues non-invasively have been invented: nuclear medicine, emission tomography, ultrasound, fluoroscopy and magnetic resonance imaging.

Today medical imaging makes it possible not only to visualise each and every organ of the human body in detail, but also to explore the way in which disease affects the organism. It shows in a striking manner and in three dimensions, myocardial contractions or cross-section images of the abdomen or of the brain; blood can be seen flowing along arteries or water along nerves fibres, the birth and death of cells within a tumour can be visualised, antibodies fighting an infection can be identified, virtual coloscopy can be performed, and the way we express our emotions—fear or love, for instance—can be mapped within the brain.

In addition, with innovations in the field of biology such as, for example, the decoding of the human genome, new prospects in terms of diagnosis and therapy have opened up. The current trend is to combine different modalities that image complementary aspects of disease, such as nuclear imaging with X-ray computed tomography or magnetic resonance. It is important not only to detect disease, but also to identify the actual disease processes, estimate the seriousness and how they are likely to respond to a given therapy so as to optimise the therapeutic treatment. It is also important to assist surgeons, allowing them to devise an operation strategy based on virtual images of their patient and then to follow the movement of their instruments in the complex environment of the human body on a real-time basis.

All these improvements cannot be developed without focused, multidisciplinary and co-ordinated action. The new generation of instruments is based on significant breakthroughs resulting from technological advances in physics, materials science, optics, electronics, information technologies, as well as in the fields of molecular biology or medical sciences.

The goal of Cerimed is to provide an environment of synergistic exchanges between the different scientific disciplines involved in medical imaging and industry. The objective is to create, within Europe, a centre with the necessary expertise and infrastructure to support an ambitious research and development program in medical imaging and prepare future generations of medical imaging systems, a decisive contribution towards solving the great public health issues of our time.

This approach must be as dynamic and interactive as possible, involving those developing imaging systems such as physicists, engineers, computer scientists and chemists, and those using imaging systems such as physicians and biologists. Industry should also become involved.

Particular emphasis should be placed on a new generation of highly sensitive molecular imaging systems with excellent spatial and temporal resolution and real multimodal capability which will make it possible to assess in the same examination molecular, functional and morphological imaging. The aim is to obtain an accurate, rapid and quantitative characterisation of pathology which will be individualised through non-invasive approaches involving as small as possible doses. This will make it possible **to improve patient care not only in terms of detection and diagnosis, but also in terms of therapy,** which will have a direct impact both on the effective treatment of disease and on the social cost.

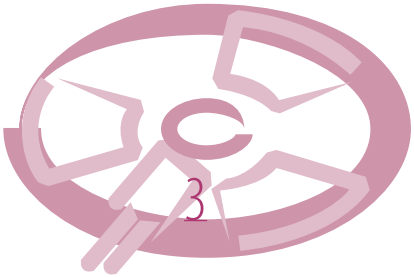
The mission of Cerimed is based on three principles:

1- meeting the increasing demand for new imaging technologies from physicians and biologists, especially in the molecular field from pre-clinical to the clinic;

2- creating a focus of of interests in Europe for medical doctors, biologists, physicists and industry representatives in the field of medical imaging;

3- creating European leadership in the field of medical imaging by providing a framework to concentrate the different existing skills in France and in Europe, which are at present strongly attracted to the United States.

In order to reach these goals, Cerimed (European Centre for Research on Medical Imaging), which has a strong multi-disciplinary character, will allow imaging techniques to progress in a co-ordinated way through the introduction of new technologies, and will facilitate the development, integration and clinical validation of new prototypes due to **the interactions within a single location between physicists, engineers, medical doctors, biologists and industry representatives.**



This molecular and multimodal imaging centre of excellence with a European perspective will be organised in six departments:

1- Technical development in the field of imaging

2- Technology transfer to clinical applications (diagnosis, therapeutic follow-up and clinical research)

3- Transfer to pre-clinical research (studies on animals)

4- Development and validation of new radiotracers

5- Education and training

6- Industry

Interacting with existing European networks, Cerimed will focus and coordinate multi-disciplinary effort in medical imaging. The goal is to provide the logistics and critical mass to implement, validate and operate complex, integrated devices. Such effort will rely heavily on existing educational institutions, emphasizing the inter-disciplinary approach and the establishment of an industry network that currently does not exist within Europe.

A-Status and Perspectives

1- Clinical applications of molecular imaging

Today, molecular imaging essentially relies on nuclear medicine. Nuclear medicine is the branch of medicine which includes all the uses of unsealed—that is, injectable or drinkable—ionizing radiation substances. These radioisotopes—or radiopharmaceuticals—can be used to diagnose or cure a disease, or in the field of biomedical research. In most cases, nuclear imaging consists in a single morpho-functional exploration of the whole body, from head to toe: radiopharmaceuticals are first injected into, then spotted within the patient's body with detectors like scintillation cameras (crystal), hence the name generally given to this technique: scintigraphy. The radiopharmaceuticals have to be as specific as possible if they are to provide information on the function and/or the metabolic activity of the targeted organ or tumour(s). Radiopharmaceuticals consist in artificial radioelements which have generally been produced in a cyclotron and which can be inserted—or not—into a vector molecule. Most scintigraphies involve labelling with Technetium-99m, a pure gamma emitter which is used in SPECT (Single Photon Emission Tomography).

In the last few years, the greatest innovation has been the possibility to use positron—also called β^+ —emitter isotopes, a technique which was made possible by the development of cyclotrons and of radiochemistry, and by progress in detectors technology. Biological molecules involved in men's or animals' metabolic functions can be synthesised by incorporating these isotopes. Their short lifetime—that is, the time it takes for their radioactivity to fall by half—is often inferior to two hours, which limits the time during which the patient is exposed to ionizing radiation, but often implies that the places where they are produced and used be geographically close to each other. These isotopes are used in PET (Positron Emission Tomography).The most commonly used radiotracer is currently ^{18}F labeled 2-fluorodeoxy-D-glucose (^{18}FDG) (Fig-A1), which is obtained by the replacement of a hydroxyl group (OH) in the 2 position of the glucose molecule with the positron-emitter radioactive ^{18}Fluor atom.

To give only a simple example taken from the field of oncology, increased metabolic activity is commonly found in malignant tumours, and most of them consume large quantities of glucose. The ^{18}FDG radiotracer concentrates in these tumours and their possible metastases, making it possible to detect them all in a single, whole-body scan (Fig-A2).

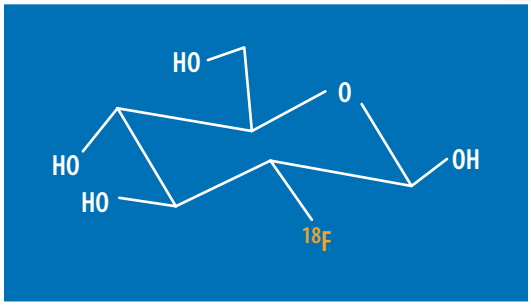


Fig-A1
Molecule of 18F FDG

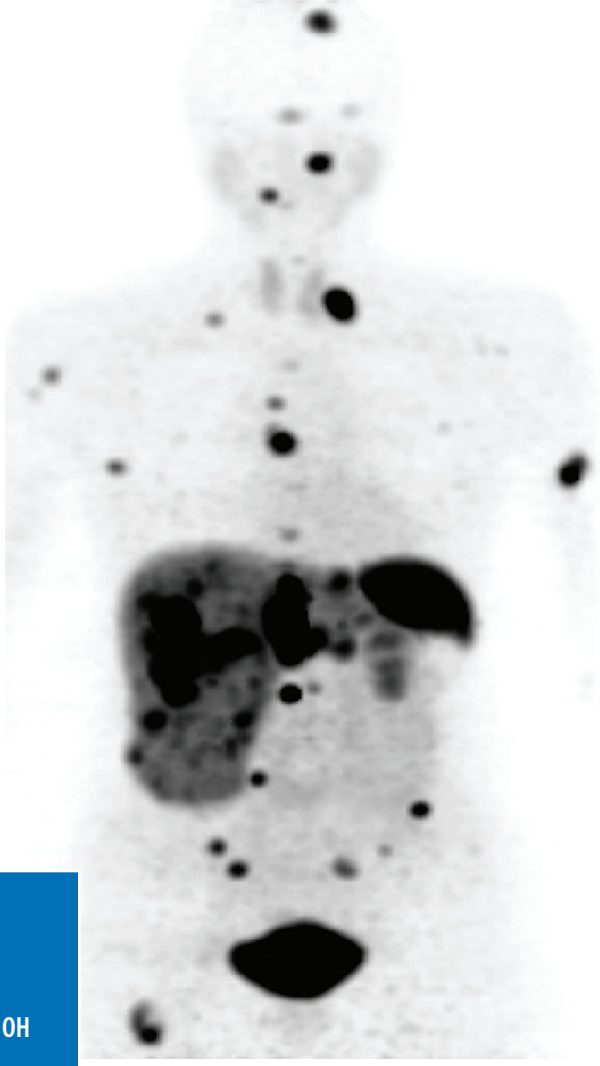


Fig-A2
PET image of a patient with multiple metastases

1-1 How muclear medicine procedures complements other imaging modalities

Radioactive probes account for about 10% of all imaging examinations each year. But they are getting more and more frequent, especially in oncology.

X-ray, magnetic resonance and ultrasound imaging are anatomical techniques which make it possible to locate and estimate the shapes, structures and sizes of organs or tumours. But only molecular imaging can provide information on the metabolic activity of an organ or a tumour in clinical routine. As the technique of molecular imaging *par excellence*, nuclear medicine can show, for instance in the oncological field, whether a persisting lesion is merely a scar, which does not absorb the pharmaceutical, or a still active tumoral tissue, which will absorb it, although the anatomical image will be the same in both cases.

But molecular imaging still lacks spatial resolution, which limits the possibility to detect sub-centimetric lesions or to locate them precisely, contrary to X-ray CT, particularly with the use of contrast agents.

Yet, the technology has evolved, with the development of PET-CT scanners which combine positron tomography to X-ray CT, the latter allowing for anatomical localisation and so-called attenuation corrections which result in higher diagnostic value PET images (Fig-A3).

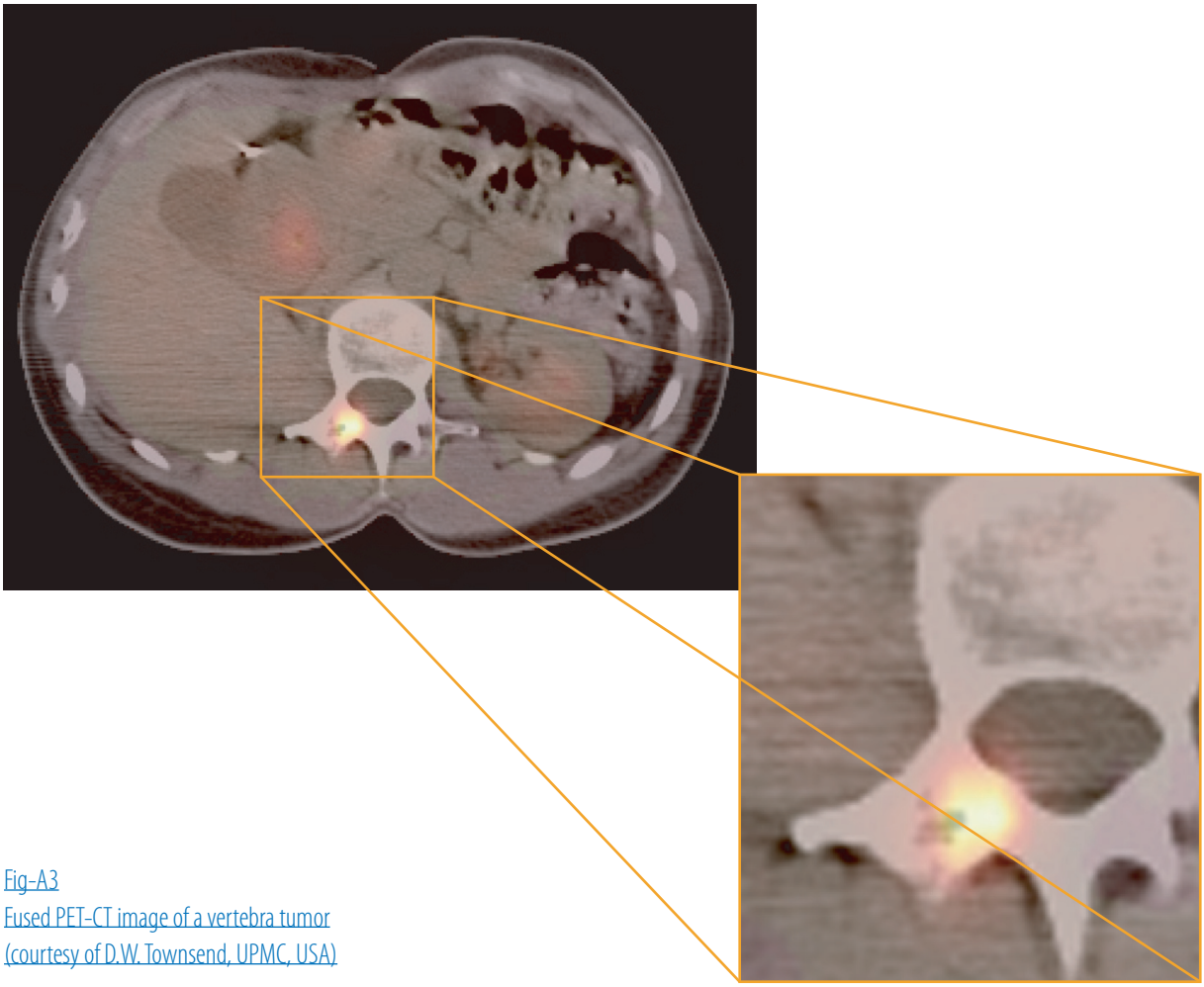


Fig-A3
Fused PET-CT image of a vertebra tumor
(courtesy of D.W. Townsend, UPMC, USA)

1-2 Current limitations

The limitations come both from the radiopharmaceuticals and from the detectors.

Radiopharmaceuticals

The most promising isotopes are positron emitters. One of the first limitations is therefore the necessity of a close-by cyclotron. Positron-labelled radiopharmaceuticals are produced through a difficult synthesis, which implies both a bad labelling yield and a high cost. Furthermore, ^{18}FDG, which is currently used, is not specific, it merely provides information on tissue metabolic activity. This implies that any process causing glucose to be overconsumed—an infection, for instance—can be mistaken for a tumoral lesion. It is therefore necessary to develop new radiopharmaceuticals specific to cell proliferation or to apoptosis (inhibition of the cell's self-destruction mechanisms).

Detectors

Scintillation cameras still use the detection principle devised by Anger 50 years ago and based on scintillating crystals. Even if digital electronics and progress in the field of electronics have much improved the collection efficiency of gamma-rays born from β^+ emission, only a small percentage at best can be detected. There are two consequences:

- relatively highly radioactive pharmaceuticals have to be administered, with significant effects on the radiological protection of patients and staff and on the cost of examinations;
- examinations last longer: a whole-body scan lasts 20 to 25 minutes, while a X-ray scan imaging only lasts 25 to 30 seconds. Besides the discomfort it generates for the patient, it also causes artefacts linked to involuntary and natural moves—breathing, cardiac and digestive.

1-3 Prospects depending on technical progress and on the availability of new tracers

Progress must be achieved in the following fields:

- **Research on new radiopharmaceuticals.** It is currently performed in at least four centres of excellence in France and in several others in Europe. It focuses on the development of new tracers, but it also aims at optimising synthesis and labelling techniques. It is very difficult and costly work, and skills in this field must not be scattered.

- **Setting up cyclotrons** in the biggest hospitals so as to deliver ^{18}FDG or other radiopharmaceuticals in the best conditions to use them both on patients and in fundamental research.
- **Research on detectors.** Detectors play a key role in imaging. Efforts must focus on gamma-ray detectors: their sensitivity has to be improved in order to obtain a combined detector which would make it possible to get information linked to X-ray absorption on the one hand and to gamma-ray emission (PET or SPECT) on the other hand by performing a single examination. The results will include:
  - quick data acquisition, so that artefacts linked to moves will be reduced and lesions will be located more precisely;
  - better spatial resolution, so that sub-centimetric lesions will be detected;
  - use of smaller doses both of X- and gamma-rays.

This research must be performed by physicists, engineers, mathematicians, biologists and medical doctors working together. It must rely on various technologies, which implies a large amount of interdisciplinarity: materials, optics, highly integrated and low-noise electronic equipment, highly parallelised intelligent acquisition architectures, calculation grids and simulation, reconstruction and image processing software.

All these improvements, both on detectors and on radiopharmaceuticals, aim at improving diagnosis, therapy and prognosis.

One of the fields which must be particularly attended to is therapeutic follow-up. Today the efficacy of a treatment can be evaluated almost only through the anatomical and clinical evolution of a pathology at more or less long term. In oncological pathology it is clearly far from enough, because evaluation takes a long time, so that inefficient heavy treatments are sometimes unnecessarily carried on, generating discomfort for the patient and heavy costs.

Molecular imaging combined to functional and anatomical imaging is beginning to address these issues, with FDG today, but certainly in a much more specific way tomorrow with the help of cell proliferation and apoptosis tracers. Due to these technical improvements, it will be possible to know, depending on the metabolic activity of the initial tumour evaluated through this kind of imaging technique, if neoadjuvant therapy has to be administered in some breast cancers for instance, and if it has to, to evaluate its impact.

But the future of molecular imaging goes much further than the mere field of oncology, which is already a vast one. It will also prove useful in cardiovascular, neurological and infectious pathologies, as well as in fundamental research, in the field of cognitive sciences for example.

2- Using molecular imaging for pre-clinical evaluation (studies on animals)

2-1 Indications and definition of the fields of interest

Although in vitro tests on cultivated cells in increasingly physiological contexts are being developed, and in spite of pressure from public opinion in favour of protecting animals, animal experimentation remains essential to validate the results of certain fundamental studies—in physiology, developmental biology, and other fields—to test the effects of newly developped drugs or to validate new therapeutic strategies, such as gene or cell therapy. More often than not, initial tests can be performed using in vitro cell models; yet, experimenting in the context of living organisms is crucial.

In more fundamental fields of research, animals provide indispensable models for the study of such physiological phenomena as cell differentiation or organ development. The possibility to create genetically-modified animals—especially mice—has opened wide new ranges of possibilities for animal experimentation. For instance, to follow the expression of a given gene, another gene coding for an imaging tracer can be put under control of the first gene's promoter. The tracer can be a fluorescent protein, such as the green fluorescent protein (GFP) and its by-products, or an enzyme catalysing a luminescent reaction. With existing imaging equipment, experiments can already be performed on small animals. The use of tracers in molecular imaging can also be considered: herpes simplex virus thymidine kinase can be associated to two-photon PET imaging, or active iode carrier to one-photon SPECT imaging, for instance. Other tracers, such as somatostatine or dopamine receptors, have already been used or are being developed in the perspective of these in-vivo approaches.

With these molecular imaging techniques many phenomena or physiological activities can be analysed and it is possible to see how specialised cells or organs work. Examples of current applications of molecular imaging are numerous; one can quote, for instance, the observation of tumour metabolic activity (^{99m}TC-Sestamibi and SPECT, or ^{18}F-FDG and PET), of iode (^{123}I or ^{99m}TcO4 and SPECT, or ^{124}I and PET), of neurotransmitters (^{123}I-FP-CIT and SPECT, or ^{18}F-Dopa and PET), of bones (^{99m}TC-Bisphosphonate and SPECT), of brain perfusion (^{99m}TC-HMPAO and SPECT) or of heart perfusion (^{99m}TC-Sestamibi or ^{201}TI and SPECT). These activity measures were generally devised using animal models; they are now often used in routine in nuclear medicine services aiming at clinical applications, but they are only beginning to be exploited in research on animal models. There are many other applications of nuclear imaging, such as detecting or locating membrane antigenes receptors, or analysing such phenomena as apoptosis, angiogenesis, cell proliferation, gene expression, etc.

In experimental pharmacology and in pre-clinical tests animal experimentation is needed above all to analyse the overall effect of a therapeutic strategy. It is also indispensable to determine the overall toxic effect of a drug. Another fact has to be taken into account: more and more genetically modified animals provide excellent models corresponding to human pathologies linked to genetic factors, for instance mice which are invalidated to study genes causing certain pathologies.

Animal models are getting increasingly sophisticated and powerful. But for the moment, most experiments are performed only on series of supposedly synchronous animals. This strategy clearly shows its limits, as statistical surveys performed on series of animals at different stages of a pathology and/or on the effects of associated therapy often prove difficult to interpret: the biological phenomena are not necessarily synchronous, or evolve differently in different individuals. This problem can be solved through individual follow-up of an animal through non-invasive imaging techniques, and the variations can thus be analysed. What is more, with the data provided by molecular imaging, a comparative study can be performed on series of clinical cases (see § A2-2). Last but not least, ethical rules encourage that as few animals as possible are sacrificed, so as to perform kinetics over a certain amount of time. With these imaging techniques, the biodistribution of molecules can also be analysed.

In the case of applications in the field of gene therapy, the operation typically consists in transferring one or several genes—for instance, a gene bringing back a lost function in the case of genetic diseases or inducing cell death in the case of oncology; most of the time, it is achieved by using viral vectors targeting precise cells. If a gene coding for imaging tracers is transferred on the same vector, all the stages of gene transfer (cell targeting and success of the vectorisation) and of the survival or elimination of targeted cells can be observed. In the case of applications in the field of cell therapy, cells are modified so as to express a tracer gene before being inserted into animals: the activity of the tracer gene makes it possible to observe what happens to the inserted cells through non-invasive imaging techniques. Here, as in previous examples, individual follow-up is crucial to interpret the results correctly.

2-2 Relative merits and complementarity with other modalities

The applications of molecular imaging are numerous: they make it possible to observe various biological functions or tracer expression through the use of isotopic markers. Nuclear imaging clearly offers a unique range of applications in the field of biological and pharmacological research. Besides, in the medical field, this non-invasive imaging technique can rely on a long experience acquired through examinations and studies performed in the numerous nuclear medicine services. The development of a few structures adapted to animal experimentation already shows the crying needs in this area. Research laboratories also take part in the development of radiotracers which should open a whole new range of applications.

There are other types of non-invasive imaging on small animals, such as chemoluminescence or fluorescence optical imaging (Fig-A4). Today, these approaches complement radioactive techniques by offering the possibility to follow expression of tracer and exogenous genes in small animals without using radioisotopes. Nevertheless, the activities which can be observed are restricted to the expression of specific exogenous proteins. Besides, for the time being, it seems difficult to develop this kind of approach on man, for two main reasons: first, because of light attenuation by tissues, which is already a problem for mice's deep-set organs and is bound to be a bigger inconvenience in the case of human subjects. It will have important consequences on the sensitivity, resolution and quantification of this kind of imaging technique, while on the other hand weak gamma-ray absorbtion does not affect it. The second reason has to do with the fact that the luminescence approach is restricted to gene or cell transfer, and is only rarely used in clinical medicine, so that developing an imaging device dedicated to man would imply large investments for extremely specific equipment. On the other hand, molecular imaging makes it possible to follow the expression of some genes by using specific tracers, and to combine these probes with functional measurements. This kind of practice is already in use in existing nuclear medicine services. Following gene or cell transfer in small animals with the help of tracer genes has already been done, and in most cases the technique can be transferred to man right away.

It is crucial to consider that by using the same approach parallel examinations can be performed on experimental models on men and animals. This common technique should make it easier to transfer pre-clinical research to clinical trials. The different forms or stages of a disease detected in man can also be found in animals with molecular imaging techniques, which would make it possible, for instance, to study the effects of various treatments on rodents relying on a diagnosis close to the one obtained in clinical medicine. For example, when trying cell implantation after heart failure the animal model consists in using rodents whose coronary artery has been ligatured. These animals' hearts do not all react in the same way. Imaging the heart perfusion makes it possible both to visualise the differences corresponding to various clinical situations and to follow the implanted cells—after inducing the expression of a tracer—and their therapeutic effects on heart functions.

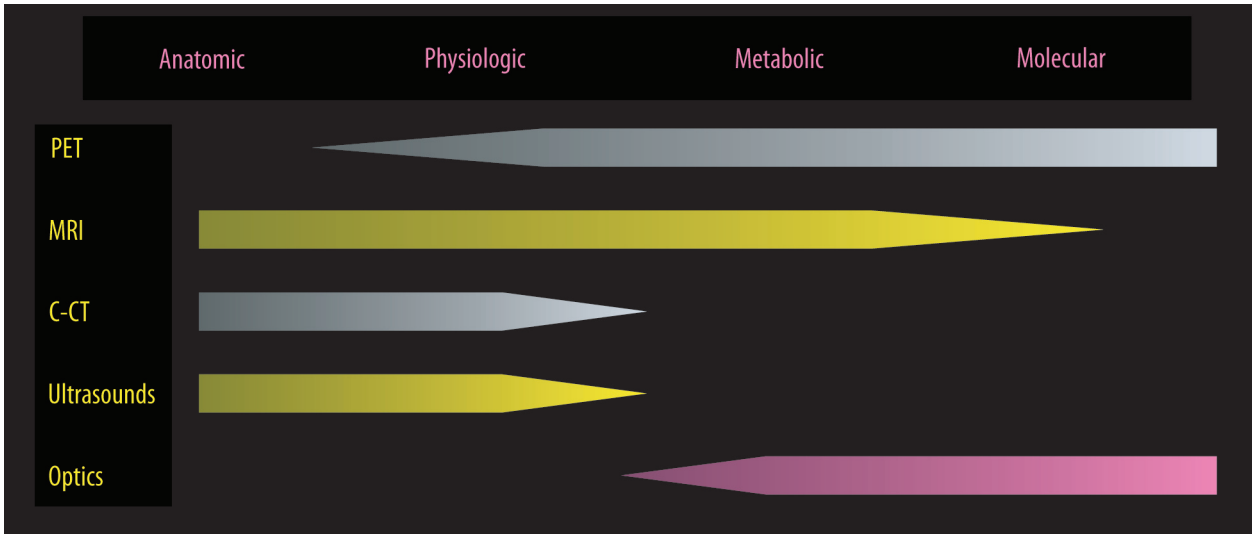


Fig-A4
Different types of non-invasive imaging

2-3 Current limitations

Here a difference will be made between SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography); these two complementary molecular imaging techniques both offer advantages and have limitations.

In SPECT, clinical cameras have a resolution of several millimetres. Considering the average size of man's organs, this resolution is often sufficient. Numerous studies can already be performed due to the sub-millimetric resolution offered by the equipment dedicated to rodents or by clinical cameras modified with pinhole collimators. Yet, it is often quite difficult to discern some of the organs of a mouse, for instance, which implies that enhancing resolution in order to be able to image small animals correctly would be an improvement. With the development of high resolution cameras, images have to be treated in the best possible way so as to correct the distortions that are bound to appear during the image acquisition stage.

The sensitivity of SPECT cameras is also crucial. When dealing with animals, it is always possible to increase radiation doses while estimating the risk for side effects that may be caused by radioactivity. Theoretically, in the usual type of collimation, better resolution means worse sensitivity. Only innovative strategies will make it possible to improve both parameters at the same time.

In SPECT imaging, it is also crucial to be able to quantify the obtained signals so as to perform biological studies. To achieve this result, the obtained signals have to be corrected in various ways, and research in this field has to be combined with the development of more powerful equipment.

PET imaging equipment is much more sensitive, with a resolution of a few millimetres, and signals can be analysed quantitatively more easily by image treatment software. Yet, there are limitations to be taken into account. First, resolution is physically limited by the average distance—1 mm in the case of ^{18}F, 1.1 mm in the case of ^{11}C, 1.5 mm in the case of ^{15}O —covered by the β^+ particle in matter before it emits the two 511 keV gamma-rays which are recorded. Besides, this distance is significantly modified by tissue thickness; for instance, in the case of 18Fluor, the distance is approximately tripled between bones and lung tissue. If resolution is improved, these differences will cause a distortion of the image. Yet, if image treatment integrates the information obtained by X-ray computed tomography (CT) this phenomenon might be compensated. Bigger imprecision would be caused by the angle of emitted gamma-rays, which has a dispersion of $\pm 0.5°$ around its average value of 180°. Finally, the isotopes which are used have very short half-lives, and they have to be synthesised nearby by a cyclotron. Labelled radiotracers have to be synthesised in conditions which take into account the isotope's half-life time. The radioelement is therefore very expensive, which is hardly compatible with the budget available to most research projects in biology.

Combined imaging associating nuclear imaging—SPECT or PET—and X-ray computed tomography is being developed. Acquiring simultaneously nuclear medecine images and X-ray CT images has several advantages: the areas identified by moelcular imaging can be located more precisely. Attenuation phenomena can be corrected precisely, and other corrections, such as partial volume effect correction, are made easier. These corrections are crucial to analyse quantitatively the radiotracer distribution. The information provided by X-ray computed tomography will also make it easier to correct the moves linked to breathing or to the animal's cardiac activity and to improve spatial resolution.

Tri-modal equipment dedicated to small animals is now sold (Gammamedica); yet, it is made up of three juxtaposed distinct instruments (SPECT, PET and X-ray CT). Imaging equipment using the same detector for several modalities would be a notable improvement. Such a detector head could make more precise alignment possible, which could prove particularly crucial if the resolution of nuclear imaging increases. Besides, with a camera which could combine SPECT and PET, all the applications of nuclear imaging, which are often complementary, could be covered. Finally, it would certainly be interesting to include other imaging techniques, such as high resolution ultrasound scanners or optical imaging.

2-4 Investigation tool for new radiopharmaceuticals

Developing high-performance imaging for small animals will open a new era for research on new radiopharmaceuticals, by making trials on rodents widespread. It would no more be necessary to work on bigger mammals, which is less convenient. Such developments will in particular make it possible to conceive imaging experiments on the numerous pathological and therapeutic models developed on small animals. Yet, investigating new radiopharmaceuticals is a complex process, and other tools and skills, such as producing radioisotopes or synthesising active organic molecules including these isotopes, are needed.

2-5 Perspectives depending on technical progress to be assessed

There are many perspectives, but it is difficult to list them, and they have already partly been introduced in preceding paragraphs. Only a few examples will be shortly listed here.

In functional trials on small animals, molecular imaging has not been used much, certainly because of the limitations that have already been mentioned. Paradoxically, it is very much used and applied to man in clinical medicine. Due to technical progress in the field of small animal imaging it will be possible to compare the results obtained for animals to those obtained for various clinical cases. The use of nuclear imaging will become widespread in fundamental research.

In pre-clinical trials geared against tumours or metastases, there are many models developed on rodents (xenografting, genetically modified mice…). For the time being, it is extremely difficult to detect small sources. High-performance molecular imaging will open new ranges for investigation in this field.

As for the uses of molecular imaging combined with tracer gene expression, improving resolution and quantification will make it possible to trace a small number of target cells: the expression of a gene in a small number of an animal's cells will be imaged.

Imaging could also become a necessary and invaluable tool to develop applications in cell or gene therapy.

3- Using molecular imaging in the pharmaceutical industry

3-1 Current situation

The pharmaceutical industry makes great use of animal experimentation to try new therapeutic agents on animal models. Because of the conception techniques of new molecular combinations by way of digital simulation, and because of very high costs—about 800 million euros are needed to develop a new drug—the candidates whose toxicity, specificity and biodistribution and pharmaco-kinetic characteristics are not adequate have to be identified at as early a stage as possible. Classical approaches are based on autoradiographic analyses: the molecule that is to be studied is injected after having been labelled with a radiotracer or a chemical reagent. The animal is then killed, frozen, and cut into fine slices which are later analysed, for instance with radio-sensitive film. This approach is not only extremely expensive, it also increasingly triggers ethical opposition on the part of the larger public, because of the large amount of animals which have to be killed, in particular in pharmaco-kinetic studies. Besides, even in supposedly synchronous groups, anatomical and physiological differences induce biases which limit the precision of such studies.

This explains why the pharmaceutical industry shows a growing interest for non invasive techniques, especially for molecular imaging. Because it is highly sensitive, PET imaging can measure the occupation rate of a molecular receptor as a function of time and of the quantity of drug which has been administered. Thus, by labelling temozolomide with ^{11}C the fixation of this anti-cancer molecule on brain tumours has been measured. And as its concentration in blood plasma was measured, the volumic distribution of the drug in the tumour could be established as a pharmacokinetic factor, relatively to its distribution in blood.

With the use of molecular imaging techniques, functional responses to therapy can also be evaluated. Such pharmaco-dynamic measures are precious, in particular in oncology, where they help optimising chemo-therapeutic treatments. Figure A5 shows a combined PET-CT image of a lung tumour which is partially necrosed at its centre after the patient responded to the treatment.

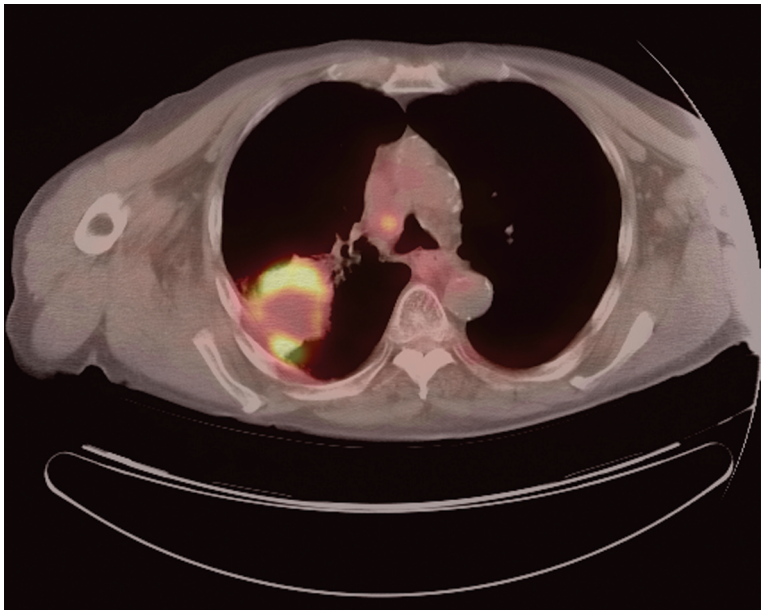


Fig-A5
PET-CT image of a lung tumor, partially necrosed after treatment
(courtesy of D.W. Townsend)

It also has to be noted that these approaches are helpful tools when use protocols and analytical procedures based on animal models have to be defined and devised for man. In spite of the limitations of current imaging equipment, big pharmaceutical laboratories have already started equipping their research institutes and working with these investigation tools. They aim at probing:

- the expression of molecular targets for therapy
- the occupation rate of these molecular targets by the drug on trial
- its concentration on the target and its evolution in time
- the mechanisms of therapeutic action
- functional response to therapy.

3-2 Perspectives depending on technical progress to be assessed

Spectacular improvements in postgenomic research probably announce deep changes in therapeutic strategies in many fields—gene or cell therapy for instance. It seems that a much more individualised approach can and must be developed. Since functional imaging helps identify how biochemical processes work, it is a precise tool which can less and less be ignored in experimental pharmaceutical research.

Just as in fundamental research, high-performance equipment will make new applications in pharmaceutical research possible, and will thus open new ranges of possibilities for pharmaceutical industry. For instance, improving the sensitivity of small animal PET scanners paves the way for quantitative PET on small animals. This is crucial for precise pharmacokinetic studies and for the control of tissue-targeting.

With the increased spatial resolution biological processes will be followed on mice or rats as precisely as on bigger animals such as cats, monkeys or pigs. As a consequence, it will be possible to work on larger groups of animals for a cheaper price, and to work on the numerous pathological and therapeutic models developed on small animals. As for gene or cell therapy strategies, improving resolution, sensitivity and quantification makes it possible to trace the expression of a gene on a smaller number of target cells.

What is more, combining functional imaging with high resolution anatomical modalities like MRI (Magnetic Resonance Imaging) or X-ray CT, will considerably increase the possibility to determine a drug's long-term action on pathological processes such as inflammation, blood flow, etc.

In short, improved sensitivity and spatial and temporal resolution, combined with real multimodal possibilities, will make it possible to test the activity of new drugs or the physio-pathological processes of disease non-invasively, killing as few animals as possible.

4- Potential technical evolutions of molecular imaging

4-1 Recapitulation of the aims of molecular imaging

Molecular imaging, in particular Positron Emission Tomography (PET), is currently being spectacularly developed. Molecular imaging consists in injecting a patient with a molecule involved in a specific metabolic function so that this molecule will preferentially be fixed on the organs or tumours where the function is at work. The molecule has been labelled beforehand with a radioisotope emitting gamma photons (Single Photon Emission Computed Tomography) or with an isotope having lost enough neutrons to emit positrons—or anti-electrons—in the case of Positron Emission Tomography (PET). In the latter case, the positron annihilates very quickly on contact with ordinary matter, emitting two gamma photons located on the same axis—called the line-of-response (LOR)—but in opposite directions, with an energy of 511 keV each. Analysing enough of these gamma photons—single (SPECT) or in pairs detected together (PET)—makes it possible to reconstruct an image of the areas (organs, tumours) where the tracer focused (Fig-A6). It is worth noting that the most often used photon emitters are ^{18}F, ^{11}C, ^{15}O, ^{13}N. ^{18}F is a Fluor isotope, which is used to replace one hydroxyl group in organic molecules like the fluoro-deoxy-glucose. ^{11}C, ^{15}O, ^{13}N are isotopes of Carbon, Oxygen and Nitrogen, the chemical elements most frequently found in organic molecules.

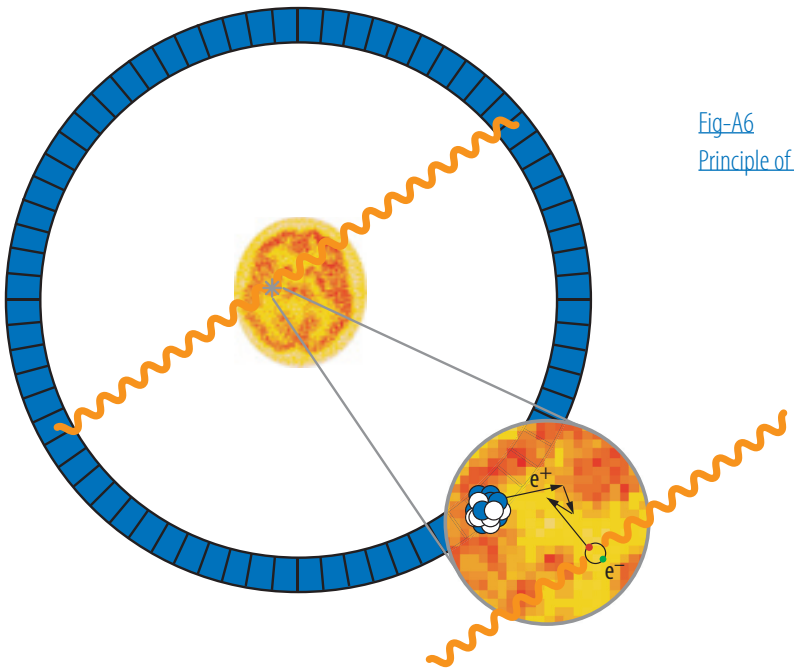


Fig-A6
Principle of PET imaging

Studying the impact of molecular imaging and its positioning regarding other non-invasive imaging modalities shows that if its functional picomolar sensitivity is several orders of magnitude bigger than magnetic resonance imaging's—which opens incredible perspectives in the field of cell and molecular imaging and for instance in the field of gene expression imaging—the detection efficiency compared to the dose injected to the patient, which is also called 'sensitivity', is strongly limited by technical constraints, and spatial resolution is still not good enough. (Table 4-1).

Table 4-1
Comparison of the performances of three imaging modalities

Imaging modality	Type of imaging	Examination duration	Spatial resolution
PET	Functional (picomolar sensitivity)	30-45'	4-6 mm
SPECT	Functional	30'	6-8 mm
MRI	Anatomical Functional (millimolar sensitivity)	10'	0.5 mm
X-ray CT	Anatomical	1'	0.5 mm

Besides, new needs arise from progress in the medical and biological fields, which implies that imaging performances have to be constantly improved. Clearly, in order to fulfil the needs of quantitative cell and molecular imaging, of dynamic studies over a certain length of time and of individualised therapy focusing on the patient's genotype, a strong demand for technical improvements will arise to address issues very similar to those that currently come up in large particle detectors, namely:

- integrating a very large number of increasingly compact measuring channels (several hundred thousands)
- extremely high acquisition rates (up to, and more than, 10 Mhz)
- bandwidths that will have to deal with data rates of more than several dozens of Gbytes/s
- a considerable number of events—several tens of millions—needed to reconstruct an image
- a huge volume of data per image—about 1000 Gbytes—and needs great calculation power to be reconstructed
- integrating technologies requiring pluridisciplinary competences within complex, compact and reliable systems.

To address these challenges innovative technologies are required; some of them are being developed for other instrumentation sectors, in various fields; one can quote:

- new dense and fast scintillating crystals or direct conversion materials
- highly segmented and compact photodetectors
- low noise and highly integrated electronic equipment
- data acquisition systems based on highly parallelised architecture
- efficient data filtering algorithms
- modern and modular simulation software based on universally recognised standards
- high performance image reconstruction and analysis algorithms.

In the last few years, there have been noticeable improvements on commercial imaging equipment, especially with new PET-CT equipment combining anatomical and functional information. But progress is far from having reached its full potential, especially as medical imaging in general, but also molecular imaging in particular, have but partially benefited from significant technological improvements in other fields like telecommunications or particle detectors. Yet, the search for a balance between the various constraints and incompatibilities and the necessary cost control will make it necessary to achieve compromises built on solid expertise in various fields differing from one another.

The challenge for functional molecular imaging lays in its capacity to quantitatively measure metabolic values. To achieve this aim, the constant goal in methodologically developing imaging equipment is to increase resolution: this means improving both the imaging system's spatial resolution, that is, its capacity to discriminate two separate objects, and the measure's signal/noise ratio, that is, how precisely a metabolic agent's concentration in a body area can be determined. The concentration depends mainly, but not only, on the imaging system's sensitivity, that is, its capacity to detect efficiently the radioactivity emitted by the patient's body, and therefore its capacity to accumulate the statistics needed to tomographically reconstruct the radiopharmaceutical tracer's distribution. Thus, the perspectives to develop molecular imaging in the future revolve around three goals:

- improving sensitivity
- improving spatial and temporal resolution
- truly integrated multimodality and multifunctionality.

4-1-1 Improving sensitivity

Sensitivity is defined as the ratio between the detected number of radioactive disintegrations and the integrated activity which was injected to the patient and fixed on the organ one wants to study. It reaches at best 2 to 3% in the case of PET scans on small animals, and less than 1% in the case of whole body PET. It must be added here that with whole body PET scanners only the patient's thorax can in fact be visualised, which is sometimes a limiting factor, for instance in oncological studies of bone metastases in limbs. In the medium term, a sensitivity of 10% for small animals and a of few % for whole body scanners seems to be a perfectly reasonable goal.

Sensitivity absolutely has to be improved for many reasons. First, examination durations have to be shortened. Today, a whole body scan lasts about 30 minutes, but it should be possible to reduce this time to a few minutes only. Thus, patients' comfort should be significantly improved. And improving the productivity of costly equipment and infrastructures would obviously have a significant impact on the cost of examinations. Shorter acquisition times would also have an effect on image quality because the impact of the patient's natural moves—breathing and cardiac activity, digestive tractus, etc.—would be significantly reduced. Quicker metabolic processes could be followed, which is crucial for pharmacokinetic studies.

In some cases, better sensitivity could help reduce injected doses, which would open new prospects for young or pregnant women and for children.

It also has to be noted that image quality is determined as much by sensitivity as by spatial resolution, since the signal-to-noise ratio per voxel is the defining factor. While improving spatial resolution by a factor 2, 16 times more noise equivalent counts are necessary if the statistical accuracy of the image is to be maintained. The capacity to acquire the image in a reasonable time—that is, as quickly as possible—depends on many factors which simultaneously influence the noise-equivalent measurement of the imaging system and of the radioactivity administered to the patient. To quote only a few, we can mention the imaging system's geometrical acceptance, the efficiency and energy resolution—thanks to which the energy selection of events can be improved, which means that in the case of a coincidence system the scattered coincidences can be discriminated more easily—, the time resolution—thanks to which, in a coincidence system, the width of the coincidence window can be reduced, which means random coincidences can be rejected more efficiently—, and the dead-time of the detectors.

On the other hand, it is obvious that looking for increasingly precise molecular signatures for the main diseases so as to devise personally targeted therapies adapted to the patient's genotype makes increasingly sensitive equipment more and more on demand. For instance, the analysis of neoplastic tissues and tumoral cells is currently mainly based on anatomical characterization by X-ray or microscopic examination of samples obtained by biopsy. With this non-invasive approach the number of biopsies should be reduced by preliminary study of the pathological nature of some tissues and by

taking into account the amplitude, the range, the localisation and the development over time of various biochemical processes in their natural environment in the human body. In this way, the nature of the pathology could be established, at least partially, through molecular imaging, using an array of radiopharmaceuticals giving information on cell proliferation (FLT), on energetic metabolism (FDG) or on aminoacid synthesis (methionine) in the various tissues. In order to achieve multitracer analysis of various biochemical or pathophysiological processes, several radioactive tracers have to be administered successively. In order to keep the doses tolerable for the patient, high-sensitivity PET scanners have to be developed.

Moreover, the quantitative aspects of molecular imaging are crucial to build new biomedical knowledge and to develop new and effective tools for diagnosis and therapy. In vivo quantitative biochemical analysis should pave the way for new non-invasive techniques to obtain pathological and pathophysiological determination of living cells much more precisely than is the case today. Molecular imaging's remarkable chemical sensitivity for concentrations of about pmole/g tissue normally makes it possible to get relevant information on molecular density in quantitative terms. Yet, technical limitations inherent to current imaging systems—non uniform response of the detector to radiation, random coincidences which create important dead-times, and many other factors which limit instrumental sensitivity—generate a lack of precision in quantitative determinations which easily reaches a 50% relative error.

To improve sensitivity, we need denser and faster scintillating crystals or direct conversion materials than available today, more compact and modular geometries, lower-noise and faster acquisition electronics, more parallelised acquisition architecture with integrated intelligence, and at least partial use of the information included in the events diffused in the patient or in the detector. Potential progress in these fields are described in the next paragraphs.

In some cases, building dedicated equipment might be the right solution to study an organ (brain, breast, prostate) in a more efficient and optimised way.

4-1-2 Improving spatial and temporal resolution

Spatial resolution reaches 1.5 mm to 2 mm at the centre of the view field of small animals PET scanners, but quickly gets worse when going away from the axis. In whole body PET it is at best 4 to 5 mm. In both cases, temporal resolution is about 5 nanoseconds. Developing and mastering modern technologies should make it possible to reach a 1-mm resolution for small animals PET or for scanners dedicated to specific organs, and a 2-mm resolution for whole body scanners. Similarly, temporal resolution should be reduced to a few hundred picoseconds.

Good spatial resolution is obviously interesting to study small animals, but also human beings: increasingly small structures which are involved in specific metabolic processes can thus be visualised. Anatomical localisation can also be more precise and fusion with CT or MRI information can be improved. But it is in the field of quantification that the improvement potential may be the most significant one. By concentrating the measured flow on the voxels which are really involved and by diminishing the blurring effects caused by insufficient spatial resolution, the dynamic sensitivity of the radiotracer's concentration measurement can be significantly improved.

To improve time resolution, use of fast scintillating crystals and acquisition electronics is needed. It has a double impact on image quality:

- as the width of the coincidence window is reduced, the number of isolated events and of random coincidences decreases linearly, reducing therefore the detector's dead-time and the image noise. Less noisy images require less filtering, increasing consequently spatial resolution and contrast;
- by the use of time-of-flight information along the line-of-response (LOR), it also makes it possible to eliminate many random coincidences and to sensibly reduce image noise.

As has already been explained in the previous paragraph, improved sensitivity has a direct impact on image quality, and therefore on actual spatial resolution because the unavoidable alterations caused by the patient's moves are reduced (shorter examination time) and because the signal-to-noise ratio per voxel is improved.

There are four factors which limit a PET camera's spatial resolution:

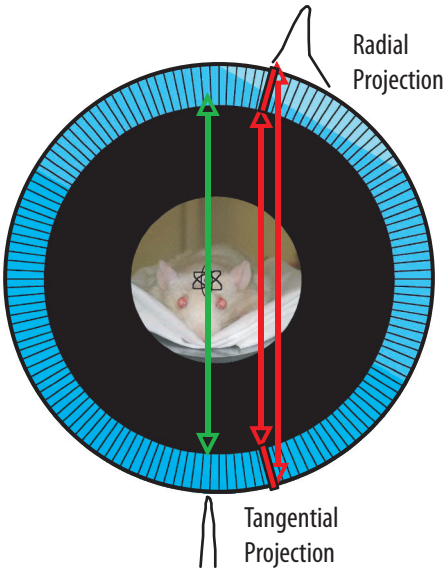
- the positron's mean free path: once the ligand has fixed itself on the organ or tumour which is to be studied, the neutron-poor radioisotope used to label it emits positrons—or anti-electrons—at a speed which depends on the isotope. As the annihilation probability of this positron with an electron belonging to the surrounding ordinary matter is at its maximum value when the positron has sufficiently slowed down, there is a difference between the emission point of the positron which is to be imaged and its annihilation point. This difference is about 1 mm in the case of ^{18}F, but it can reach several mm for other isotopes—4.5 mm for ^{82}Rb, for instance. This consequence is often considered as an intrinsic physical limitation of PET spatial resolution, but it can be significantly attenuated by the use of various electromagnetic artifices. For instance, the positron's trajectory usually revolves around the lines of a magnetic field—which is naturally present in the case of a combined PET-MRI camera—, which therefore reduces its actual free motion. It also has to be noted that positron annihilation probability as a function of its speed is a well-known function but it is not exploited today in image reconstruction algorithms.

– Non-colinearity of the two gamma photons deriving from positron annihilation: according to the laws of kinetics the two gamma-rays resulting from the annihilation of a motionless positron have to be emitted on the same line-of-response (LOR) in opposite directions. In actual practice the positron often still has residual kinetic energy left at the moment when it is annihilated, which causes an average acolinearity dispersion of the two gamma photons of about 0.5° at full width half maximum. The error in the reconstruction of the emission point varies like the square of the scanner's radius. In this regard, it will be a great advantage to build equipment dedicated to the study of specific organs whose detectors can come as close as possible to the areas to be studied. Besides, exploiting statistical information on positron annihilation should make it possible, here again, to reduce the consequences of this imprecision.

– Size of the detection crystal (or pixel): today, it is the determining factor in spatial resolution limitation. Typically, the reconstruction error of each LOR is given by the half width of each pixel. It is mainly through the use of higher-density crystals and highly segmented photodetectors that spatial resolution can be improved. A significant increase in the number of channels, resulting from finer detector segmentation, implies that important efforts have to be made in order to find cheap solutions at the level of photodetectors and readout electronics. Difficult engineering problems have to be solved in order to integrate all the channels in a small volume and to keep the electronic equipment's thermal dissipation at an acceptable level.

– Parallaxe effect: good spatial resolution has to be obtained not only on the axis, but also on sufficient patient volume. The depth of detecting crystals is limited by the density of the crystals and it cannot be reduced without altering the detector's sensitivity. As the conversion point of the gamma photon in the crystal is not known, spatial resolution gets worse when getting away from the scanner axis. This effect, which is known as parallaxe error, is all the more important as the scanner's radius is small (Fig-A7). To limit this effect, one solution is to segment crystals in depth in a so-called phoswich configuration. If pertinent emission wavelength parameters and decay time are chosen for the crystals to be used, the reading electronics can differentiate a conversion occurring in the front part or in the back part of the phoswich. Spatial resolution is therefore much more homogeneous on a larger field of view (Fig-A8).

Fig-A7
Parallaxe error



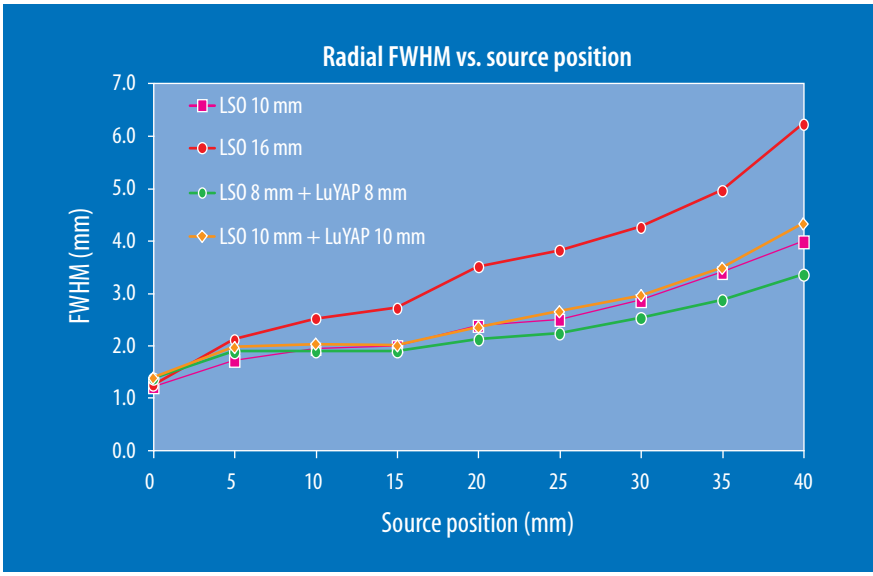


Fig-A8
Spatial resolution with and without phoswich
(Crystal Clear, UNIL)

4-1-3 Multimodality and multifunctionality

The spectacular development of bimodal acquisition systems, for metabolic, functional and anatomical data registration, like PET-CT type equipment—700 existing machines as of today—, is radically modifying the managing of the patients due to increased precision in diagnosis and results interpretation. Although this approach is just starting to be developed, it helps to diminish significantly the number and the total duration of imaging scans for a single patient and to improve interpretation quality.

Simultaneous PET-CT imaging brings other benefits in the planning of radiotherapy, which is a promising area for research and clinical applications. The principle of radiation therapies is to modulate intensity according to the spatial distribution of the area to be treated (Intensity-Modulated Radiation Therapy, known as IMRT). Putting together PET images, which provide information on the metabolic extension and heterogeneity of tumoral tissues, and X-ray CT images, which provide precise structural location, makes it possible to draw an irradiation map helping to focus therapy on the areas where the tumour is particularly active. In these conditions, it seems reasonable to bear systems integration in mind when designing the improvements to be made on imaging machines.

The most frequent equipment combines a PET scanner and a X-ray CT scanner. It actually consists in merging images acquired with two distinct imaging devices (which are assembled in the same box, though) at two very close, but not simultaneous, moments. The devices are generally not mounted on the same rotary holder. The result is imprecision caused by image adjusting and to external and internal moves on the part of the patient. Simultaneous recording of anatomical (CT) and functional (PET and/or SPECT) information by the same reading head is far from impossible, since, for instance, improvements in microelectronics allow to integrate a photodetector or a photoconductor directly into a CMOS chip. Besides, the high sensitivity of modern ASIC chips makes it possible to develop electronic reading canals able to count each individual event, which could be perfectly appropriate for X-ray CT, PET and SPECT data acquisition. This is a particularly interesting perspective, because it would make it possible to correct attenuation and partial volume effect more precisely. X-ray data (CT) provide crucial information helping to correct the unavoidable attenuation factors from the patient's body in PET images and to improve image quality and diminish the influence of artefacts. Partial volume effect is caused by PET's limited spatial resolution, which dilutes information from small hot spots onto the whole concerned voxel(s). CT information, whose anatomical precision is much better, helps to correct, at least partially, these negative effects. But such correction is made difficult if both imaging systems acquire data in distinct, poorly correlated spaces. In the case of attenuation and partial volume correction, it is crucial to record both data sets as simultaneously as possible so as to guarantee perfect image superposition.

Because it avoids duplication of data acquisition and image reconstruction functions, and because it helps to diminish the number of imaging examinations and to shorten total examination duration, an integrated approach of PET-CT imaging offers both opportunities to reduce costs and to improve information quality.

Another way of obtaining images associating great anatomical precision and high sensitivity functional information is to merge magnetic resonance (MRI) and PET images. As in the case of PET-CT, and for the same reasons, both data sets have to be acquired as simultaneously as possible, even if a universal acquisition system cannot be considered here because of the huge differences between these two modalities. The PET-MRI approach is particularly promising to study the brain, for which image adjusting is easier, because of MRI's essential contribution in this field.

Besides, BOLD contrast MRI, which relies on the variation of blood oxygenation level, proves more and more promising every day as a tracer of neuronal activity in functional MRI imaging. Combining this approach with PET functional imaging using various ligands (dopamine, serotonine, acetylcholine, glutamates, opiates, etc.) opens new ranges of possibilities to better understand fundamental neurotransmission mechanisms in the brain.

Yet, a number of significant technological problems arise from recording almost simultaneously MRI and PET images; these problems are mainly caused by the presence of powerful magnetic fields in MRI, with a high homogeneity constraint. To combine the two systems, innovating technologies are needed. It is particularly the case for the photodetectors used in PET scanners, since classical photomultipliers do not work in a magnetic field. Significant research and development efforts, initiated to answer demand from the field of particles physics, are being made to develop avalanche photodiode matrices which should answer this need; these new detectors have another advantage: they are extremely compact and require bias voltage of only a few hundred volts, while photomultipliers need kilovolts. Besides, conducting or ferromagnetic materials have to be carefully avoided because they could alter the homogeneity of the MRI's magnetic field. Other technical difficulties which have to be solved are linked with gradient coils and to MRI's radiofrequency fields, which require protection against Foucault currents and electromagnetic noise.

Finally, let us state that through the combination of PET and SPECT imaging and through the intelligent use of the labelling of various ligands used in PET imaging, a really multifunctional approach of imaging can be considered. Because it makes it possible not only to detect, but also to identify tumoral tissues simultaneously, such an approach could prove extremely useful in other fields than cognitive sciences.

4-2 New conversion materials

4-2-1 Scintillating crystals

The scintillating crystals used in PET scanners have to be dense, with a high atomic number, so as to optimise detection efficiency, and fast, so as to reduce the dead-time. The width of the coincidence window can therefore be reduced, thus allowing to eliminate as many random coincidences as possible, to make the use of time-of-flight information possible and to increase the relevant information contained in the data so as to reconstruct a less noisy image. They also have to have sufficient energy resolution to discriminate between the right events and the ones which suffered from diffusions in the patient's body or in certain parts of the detector, so as to eliminate or correct them.

Almost all the PET scanners which were sold until recently were based on BGO crystal detecting arrays, which have the advantage of being very dense (7.1 g/cm^3) and of having the highest average atomic number known to this day for a scintillator (75), and therefore a high detection sensitivity. But their main flaw is their slowness: 300 ns for the decay time constant of the scintillating light. As a result, these scanners work with a sensitivity of about 1000 kcps/μCi/ml with a coincidence window of about 10 ns and a proportion of diffused events of more than 30%. A new generation of scanners is now being developed; these scanners are based on crystals which are about 10 times faster than BGO and which integrate the possibilities of determining interaction depth in the crystals with phoswich technology (see § A4-1-2). Sensitivity should thus be improved by about one order of magnitude and spatial resolution by a factor 2 or 3, on condition that reading electronics adapted to these new performances is simultaneously developed.

In the last ten years, many groups, among which the Crystal Clear collaboration, have been making many efforts for pluridisciplinary work involving experts in various aspects of materials sciences—crystallography, solid-state physics, luminescence, photonics, defects in solids—as well as industries, in order to develop new scintillating materials adapted to the demand for increasingly efficient detectors in physics and medical imaging. Innovating crystals, such as those from the family of Lutetium perovskites (LuAP), have been developed and are now being produced industrially. Their properties are similar to, and complementary with, those of LSO (Lutetium orthosilicate) which is starting to be introduced into new generation scanners. LuAP can be used on its own, or it can be combined in a particularly optimal way to LSO to solve the tricky problem of determining interaction depth. LuAP is particularly attractive for PET applications because of its high—and unmatched to this day—density of 8.34 g/cm^3 and of its response time (17ns) which is twenty times faster than BGO's, and even twice faster than LSO's. Although its luminous yield is about twice weaker than LSO's, the linearity of its response as a function of energy is much superior, which results in an energy resolution at least equivalent to, if not better than, LSO's. Besides, everything seems to show that technological progress in producing this crystal industrially should sensibly increase its luminous yield, and thus improve its energy resolution even more. This crystal also has the interesting property of existing in several variants whose optical parameters are different and vary as a function of the quantity of Yttrium atoms which can be substituted to Lutetium atoms, which helps optimise its performances according to the application (Fig-A9).

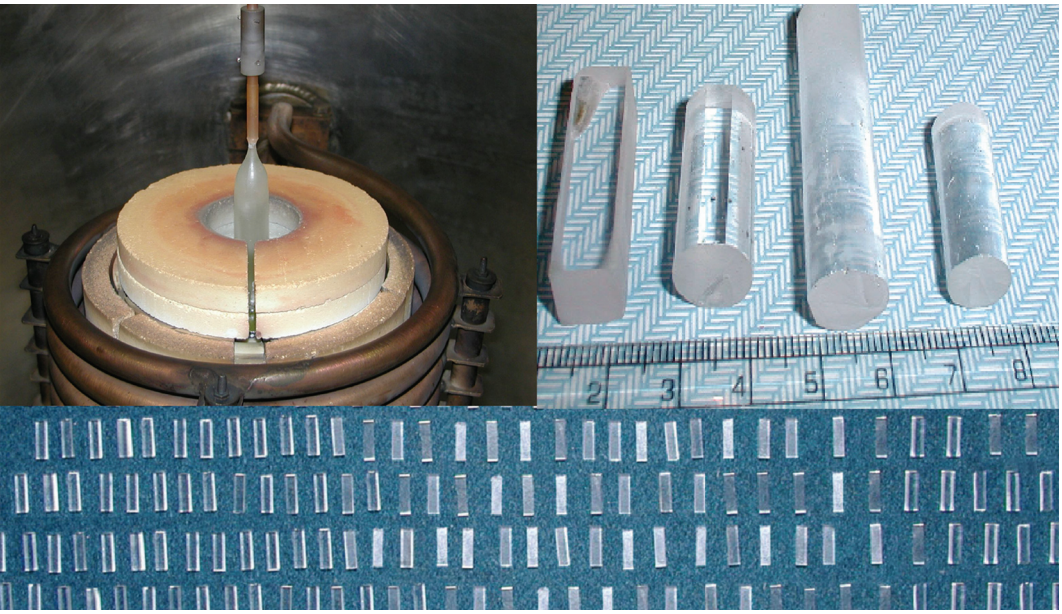


Fig-A9
LuYAP crystals produced in Bogoroditsk, Russia (Crystal Clear, CERN)

The main scintillating crystals which are currently available or which are being developed are presented in Table 4-2, along with their main characteristics.

But significant efforts still have to be made, in particular in the following fields:

- improving the performances of existing materials, in particular for Lutetium, Gadolinium and Yttrium perovskites and the silicates of these components,
- developing strategies aiming at identifying the main production cost drivers of these crystals, and trying to reduce them,
- exploring new materials, in particular those based on Hafnium, Scandium and Zirconium, which are particularly promising in terms of density, speed and light yield,
- developing innovating geometries taking into account progress in the field of photodetectors and acquisition electronics and making it possible to get away from an approach based on always finer pixels, which would provide interesting possibilities in the field of integrated multimodality, help to save money on pixel making and to get better hermeticity, so that sensitivity would be improved.

Table 4-2
Scintillators used in medical imaging or in development.
Particularly interesting values are quoted in red.

Scintillator	Type	Density (g/cm^3)	Light Yield (Ph/MeV)	Peak emission wavelength (nm)	Decay time (ns)	Hygroscopic	Application
NaI:Tl	crystal	3,67	38000	415	230	Yes	SPECT
CsI:Tl	crystal	4,51	54000	550	1000	Slightly	SPECT, CT
CWO	crystal	7,9	28000	470/540	20000/5000	No	CT
(Y,Gd)2O3:Eu	céramic	5,9	19000	610	1000	No	CT
Gd2O2S:Pr,Ce,F	céramic	7,34	21000	520	3000	No	CT
BGO	crystal	7,13	9000	480	300	No	PET
GSO:Ce	crystal	6,7	12500	440	60	No	PET
LSO:Ce	crystal	7,4	27000	420	40	No	PET
LuAP:Ce	crystal	8,34	10000	365	17	No	PET
LaBr3:Ce	crystal	5,29	61000	358	35	Very	PET

4-2-2 Photoconducting materials

Because extreme density is needed to increase the detection efficiency of the gamma-ray converter, semi-conductor technology, allowing to directly convert the energy of the gamma photons into electric charge carriers (electrons and holes) without the need of scintillation light, has not yet been applied to PET imaging. Most of the semi-conducting materials which are known and used industrially, such as Silicon, are not dense enough and do not have sufficient stopping power for 511 KeV gammas (density 2.33 g/cm^3 and atomic number 14, compared with, for instance, BGO's density, 7.13 g/cm^3, and average atomic number, 75). But this technique is used in X-ray imaging and makes the acquisition of high resolution digital images possible (Fig-A10).

To use the same principle in gamma imaging, multi-layer systems can of course be considered to, but to this day integrating a huge number of channels in these conditions has laid unsolvable problems, especially in terms of connexions. Yet interesting perspectives to solve a number of these problems have been opened by recent improvements, such as the possibility to couple semi-conductors with their reading electronics (Fig-A11) or to put semi-conductor materials directly onto ASIC chips, making it possible to read a huge number of channels on a very small surface quickly and with low noise.

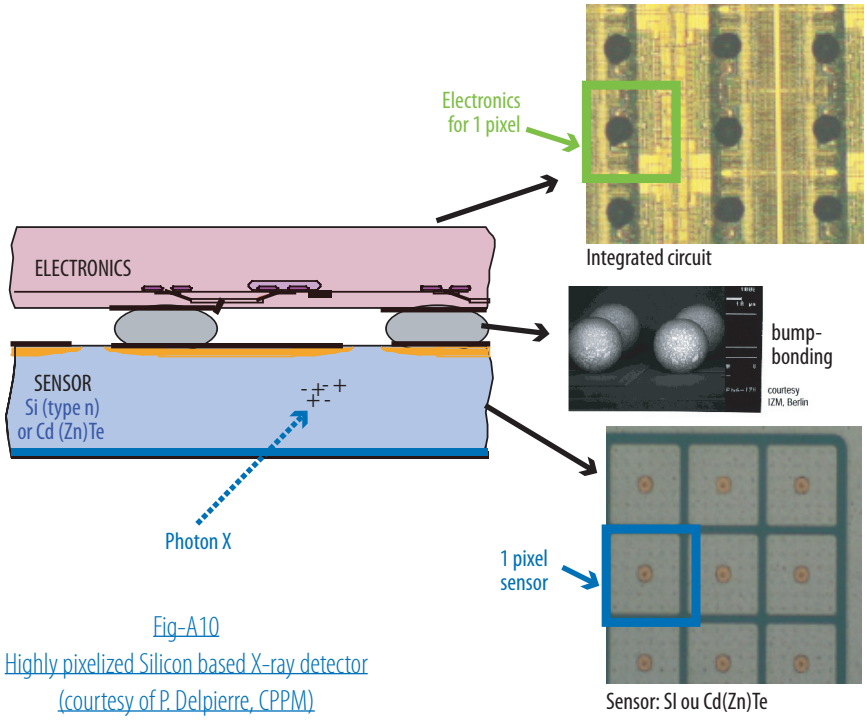


Fig-A10
Highly pixelized Silicon based X-ray detector
(courtesy of P. Delpierre, CPPM)

New semi-conducting materials much denser than Silicon are also being developed: Gallium Arsenide (GaAs), with a density of 5.32 g/cm^3 and an average atomic number of 31, Cadmium Telluride (CdTe), with a density of 5.85 g/cm^3 or Cadmium and Zinc Telluride (CdZnTe, or CZT), with a density of 5.78 g/cm^3 but whose atomic number is higher, 49 instead of 32. One of these materials is particularly attractive because of its density and of the heavy atoms which constitute it: Mercuric Iodide (HgI_2). With a density of 6.4 g/cm^3 and an average atomic number of 62, it nearly equals the stopping power of the best scintillating crystals (BGO, LSO and LuAP). It can be used with a low polarisation voltage at room temperature and can be produced by relatively cheap vacuum deposition processes. The picture shown in Fig-A11 shows an example of polycrystalline growth in columnar structure by vacuum vapour deposition.

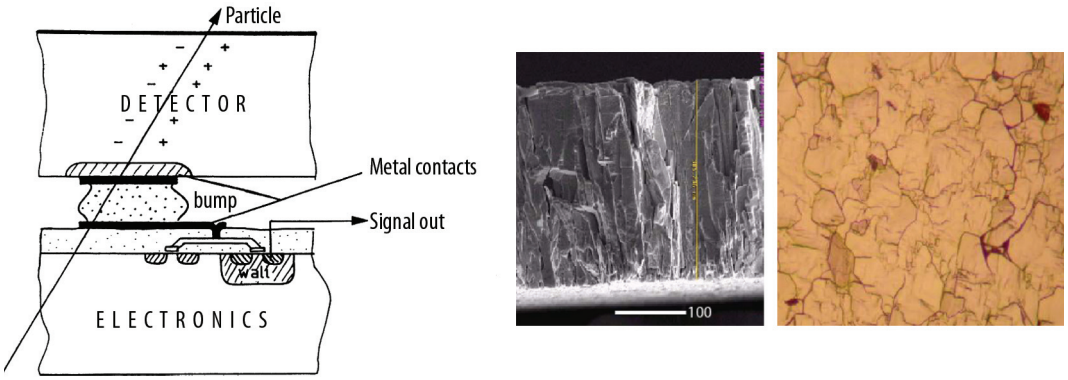


Fig-A11
Principle of a photoconductor coupled to its readout electronics and polycrystalline HgI2 deposited on a glass substrate
(Courtesy of P. Jarron, CERN)

With these materials, which are deposited directly onto a chip integrating a large number of readout and signal-processing channels, a reduction of the costs of systems which are much more compact and much more sensitive than the existing ones seems to be possible. This approach makes feasible to build a detecting head which would be potentially cheap and three-dimensionally segmented, that is to say with really multimodal capacity. It has to be noted here that this technology is fully compatible with MRI. About one millimetre thick layers are now feasible, even if many problems remain to be solved, especially regarding the industrial production of sufficiently homogeneous material and the efficiency and time of collection of the charges produced by gamma-ray conversion.

To explore all these techniques in order to determine those which can be successfully combined and to significantly improve imaging in terms of performance and of costs, a pluridisciplinary approach and a combination of various expertises in a number of fields—designing of fast, low-noise and highly integrated ASIC, micro- and nano-electronic technologies, deposition of photoconductors and photo-detectors onto CMOS chips, photonics, computer modelling—are needed.

4-3 New photodetectors

All commercial PET scanners are based on the use of specific sensors which convert the light pulses emitted by scintillating crystals into electric signals.

In whatever field of nuclear medicine and radiology (planar scintigraphy, X-ray CT or PET), the basic technique to detect ionizing radiations uses scintillators to convert X- or gamma-rays into light which is then turned into electric signal by a specific sensor called photodetector. Up to now, the standard equipment sold by commercial firms is equipped with photomultiplier tubes (PMT) used as light converter sensors. They are very efficient but they are also expensive and voluminous. Hamamatsu (Japan) and Photonis (France) provide almost all the PMTs sold today. These technologically mature products have reached their limits in terms of dimension, compactness, efficiency and cost. But diminution in size of scintillating pixels along with an increase in their number could limit their use in the future.

Recently, new compact photodetectors have been developped, for instance hybrid photodetectors (HPD), photodiodes and avalanche photodiodes, allowing to significantly improve sensitivity and spatial resolution.

This approach is already used in some X-ray CT systems where the PMTs are replaced by photodiodes. If photomultipliers are also replaced by semi-conductor sensors in PET imaging, each instrument in a combined PET-CT scanners can be miniaturised.

4-3-1 Flat and pixelized photomultipliers

In current PET systems several scintillating pixels are readout through a single photomultiplier channel, which can create jamming and therefore ambiguities and dead-times in the downstream readout electronics. The ultimate success in terms of spatial resolution, sensitivity and signal-to-noise ratio would consist in segmenting scintillating crystals more finely and, if possible, coupling them directly—one to one—with highly pixelised photodetectors with a geometry making three-dimensional reconstruction of the interaction point of the annihilation possible. This principle is already applied in numerous microPET systems for small animals.

4-3-2 Avalanche photodiodes

Avalanche photodiodes are semi-conductors which convert light directly into electric pulses. Large-scale use (120000) of avalanche photodiodes (APD) in a large crystal calorimeter of the CMS experiment at the LHC (CERN), suggests that in the future, this technique might be the only one which could fulfil the technical and economic constraints of a whole-body PET.

There are numerous advantages to avalanche photodiodes:

- because of their great compactness, they allow a large integration level for the electronic readout system and there can be as little space as possible between the various crystals.
- They convert light very efficiently, typically 3 times better than photomultipliers.
- APD arrays with many pixels are easy to make without significantly increasing cost, which is proportional to their size in a large measure.
- They can be produced in great numbers for a small cost.
- They are not sensitive to the effects of the magnetic field, which could make PET-MRI multimodality possible.

Yet, their gain is currently much inferior to photomultiplier tubes': signal amplification and weak sensitivity to electromagnetic environment are required.

Current APD with gains ranging from 100 to 1000 coupled with luminous scintillators like LSO showed their possible applications in small animals CT.

Because of their numerous advantages, APD are very attractive for new generation PET.

Today, almost a single company, Hamamatsu, can produce large numbers of APD with adequate characteristics. Other semiconductor companies, especially in Europe, could also develop this activity.

Other photodetectors based on semi-conductors like SiPMT (Silicon Photomultipliers) are now being developed for particles physics. It is too early to know whether they can be applied to the medical field, but their intrinsic conceptual characteristics seem most promising (high pixelisation and high gain).

4-3-3 Hybrid detectors

The consequence of subdividing crystals into small pixels is a significant increase in the number of photodetector channels, so that they have to be coupled with highly pixelised sensors with sufficient gain, excellent linearity and no cross talk.

Hybrid Photon Detectors (HPD) have many such characteristics, so that they could make good sensors in the future. They can be made with compact dimensions, with a spatial segmentation of about one millimetre which could be adjusted exactly to the size of scintillating pixels. With an extra fine sapphire window, the photodetector and the scintillating material can be perfectly coupled.

Most of the limitations of conventional and multi-anode photomultipliers—gain variation and cell-to-cell coupling effects, for instance—are almost eliminated by this technology.

These last few years, Europe, under the leadership of CERN, has built the necessary infrastructures to achieve the expertise needed for optimising this photodetector. The specific needs of medical imaging, such as random electronic activation, are being developed and integrated.

4-4 Highly integrated and low-noise electronics

European laboratories and institutes of particles physics are experienced in designing and setting up high-performance and highly-integrated circuits to treat low-noise analogical signals with many channels; these characteristics are very close to the ones PET imagers need.

Treating the signals emitted by the sensors is an essential element of the electronic chain. Because of the multiplication of readout channels and of the use of semi-conductor sensors, extremely low-noise and high-speed electronic circuits have to be developed. Technologies have evolved impressively in this field, which makes it possible to realise crucial improvements both in terms of integration and miniaturisation and in terms of cost. This electronics is using integrated circuits of the VLSI CMOS type. Medical imaging should also be able to benefit from spectacular progress in high-scale integration of electronic channels with complex functions and highly-segmented sensors. The concept of a hybrid detector in which each pixel is directly integrated to its readout electronics opens whole new perspectives in the conception and architecture of new imaging systems.

4-5 Intelligent and triggerable data acquisition systems

The acquisition system's function is to select the interesting events detected by the sensors in real time and as quickly as possible. Small-amplitude pulses coming from different sources (thermal and electric) should be ignored when treating the electronic chain. The triggering system has a double goal: first, it has to discriminate between the interesting events—coming from real X- or gamma-ray interactions to be analysed by the detector—and the various background noises, and then it has to start the data transferring process between the electronic boards and the computer(s) where these events will be treated to obtain the final image. These data are produced randomly, and they cannot be anticipated. Real-time, quick signal analysis is the only way for decision taking without any loss of information. In medical imaging, most of the radioactive 'real events' are triggered by analysis of the amplitudes and temporal data produced by each sensor. Specifically designed circuits compare the amplitude of each analogical signal with a threshold reference value in order to trigger digitization of the ones which are above the threshold.

Downstream, other circuits fabricate the topological and temporal combinatorial logic of all the digital signals so as to finally select the events. In the case of a PET, two topologically-opposed signals with the same amplitude and correlated in a time window are needed. The width of the window, which is defined directly by sensor signals, determines the amount of random coincidences which contaminate the final image (diminution of signal-to-noise ratio).

Finally, the selected signals are labelled and transferred to the final analysis system which is made out of storage memories, treatment units and visualisation consoles. In this so-called acquisition system, data will be selected, standardised, organized, manipulated, corrected, treated with more or less complex algorithms and finally presented as an image file.

In conventionally-architectured data acquisition systems, data treatment is performed sequentially and the system does not take in any event before the one which is being treated is over; piling up is thus avoided, but dead-times—more or less long—occur at each treatment stage. The efficiency of data collection is thus strongly affected by these dead-times which come from three main sources: first, the sensor and the electronics it uses to generate an electronic pulse, second, the analogic-to-digital conversion of this signal, and third, the logic treatment (in general, the main one).

Today other architectures minimising, or even suppressing, these dead-times, and thus increasing collection efficiency, have been developed. With them, more elaborate signal treatment is possible since the form of the signal is analysed, so that its amplitude and time are determined very precisely. This architecture has been used successfully in fundamental research experiments in particles physics. Basically, it consists in sampling each sensor's signal and immediately treating the acquired data in real time. A frequency of at least 50 MHz seems both reasonable and compatible with the length of the

signals produced by the sensors associated to the detectors—LSO crystals for instance. What makes such a concept interesting is that it uses all the data in the signal by analysing its form in terms of amplitude and time with a digital filter. The data are then treated directly in combinatorial logic at a frequency equivalent to the initial sampling's, which limits the number of possible combinations to a few dozens at most. Meanwhile the primary digitalised data are stored in buffer memories, waiting for the quick decision to keep or to eliminate this configuration, called 'event'. In this way, all the useless data or events, such as random coincidences or coincidences coming from outside the human range, are eliminated, and treatment and data-transferring problems are greatly simplified. This treatment technique, in real time and with no dead-time, called 'pipeline', is today completely mastered and it has been systematically applied to selection and data-transferring logics in physics experiments for many years.

A further improvement has been added recently to fulfil the extremely ambitious requirements of the Large Hadron Collider (LHC) at CERN, for which time and fast data treatment constraints have become even stricter. It seems obvious that such an architectural concept can be easily adapted to electronics for PET and other imaging devices. The only additional constraint has to do with the random nature of the source's decay phenomena. Based on primary analysis of PET's current performances, possible gain can be estimated about 3 or 5 times better in terms of efficiency, which would have a huge impact on the use of PET in the future. In clinic, examination duration, tracer activity and exploitation costs would be reduced. Besides, diagnosis quality would be improved by increased sensitivity, dynamic range and better image resolution. Moreover, the technique of time-of-flight measurement of each emitted photon could be naturally integrated with maximum efficiency by the use of such architecture, so that the coincidence window would be reduced to its theoretical minimum of about 500 picoseconds.

Although the pipeline technique seems more complex and more expensive than the conventional one, improvements in basic electronics (ASIC and FPGA) in terms of integration and cost suggest that in a very close future medical PET entirely based on this concept might be conceived. Similarly, progress in terms of communication and network between the electronic system and the analysis system (computer) is no more a limiting factor for fast data transfer (1 Gbits/s). Finally, with the parallelization of processors in cheap PC clusters (processor farms), almost unlimited calculation power is now available.

The acquisition system must no more be a limiting factor in medical imaging performances, as is the case today in many commercial systems. With the technological developments and progress in the field of electronic components and calculators combined with new architectures, new systems with the capabilities needed for the new generation of medical imagers such as whole-body PET scanners will be developed. Yet, this passage from 'the state of art' to clinical reality requires many further developments and adaptations.

4-6 Simulation software

Simulation through the Monte Carlo method is an essential tool to help developing new detectors used for medical imaging. Simulating various detection configurations is crucial if we want to predict and optimise the performances of an imaging system, validate new tomographic reconstruction algorithms or decide how to correct data.

Many simulation tools have been developed more or less successfully to try and solve the problems met by medical imaging. Besides, efficient versatile generic simulation tools have been developed for particles physics, for instance Geant3 at CERN, EGS4 at SLAC or MCNP at Los Alamos National Laboratory. More recently, the development of Geant4, based on oriented-object technology, has made it possible to include efficient geometrical simulation and visualisation tools. GATE was developed on this basis; it is a simulation platform written specifically to produce computer models of imaging systems, through which time-dependent phenomena—detector motion, isotope radioactive decay, dead-time phenomena—can be followed (Fig-A12). This new simulation tool, developed, validated and documented by the OpenGATE collaboration, where about twenty laboratories of medical and particles physics are gathered, is freely available on the Internet and is currently used by a community of more than 200 scientists all over the world (http://www.opengatecollaboration.org).

The future of this simulation tool will strongly depend on the part played by Monte Carlo simulation in nuclear imaging, and possibly in other disciplines like dosimetry or radiotherapy, but also on the capacity of researchers in medical imaging to get organised in order to maintain and develop this software.

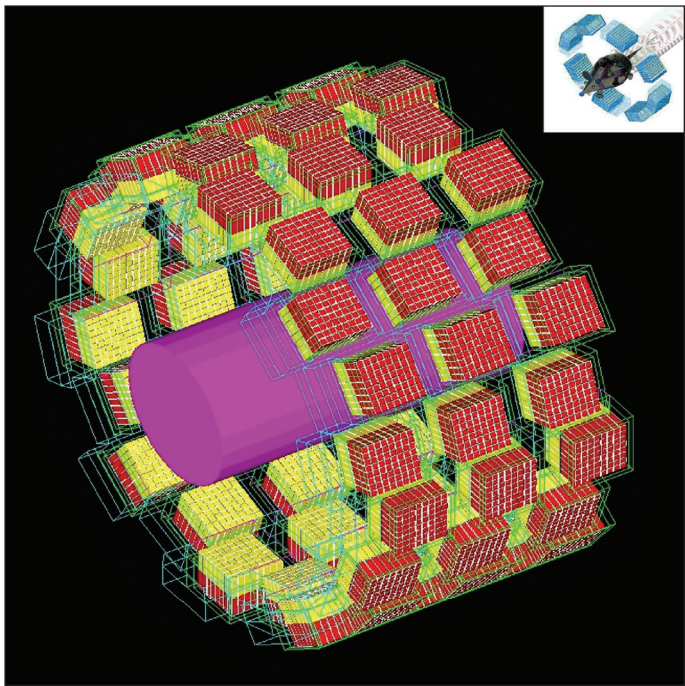


Fig-A12
Simulation of the ClearPET® with GATE
(Crystal Clear, UNIL)

4-7 New reconstruction and visualisation algorithms

The data provided by transmission and emission tomographs mainly make it possible to work on projections of the image to be reconstructed. The images are then reconstructed from the projections with tomographic reconstruction methods. There are two different possible approaches to deal with tomographic reconstruction problems. The first one is analytical and consists in treating the measured projections as if they were perfect mathematical projections. In this case, it is necessary to make a number of hypotheses on linearity and continuity, but the data, noised and often incomplete, will sometimes hardly fulfil these requirements, so that they will have to be corrected as much as possible. The second approach is phenomenological, and it consists in trying to modelize the measuring process as precisely as possible, using a probability matrix which has to be reversed through iterative algebraic techniques. In this case, it is also possible to take the statistical nature of measurements into account by using tools borrowed from statistical mechanics (Fig-A13).

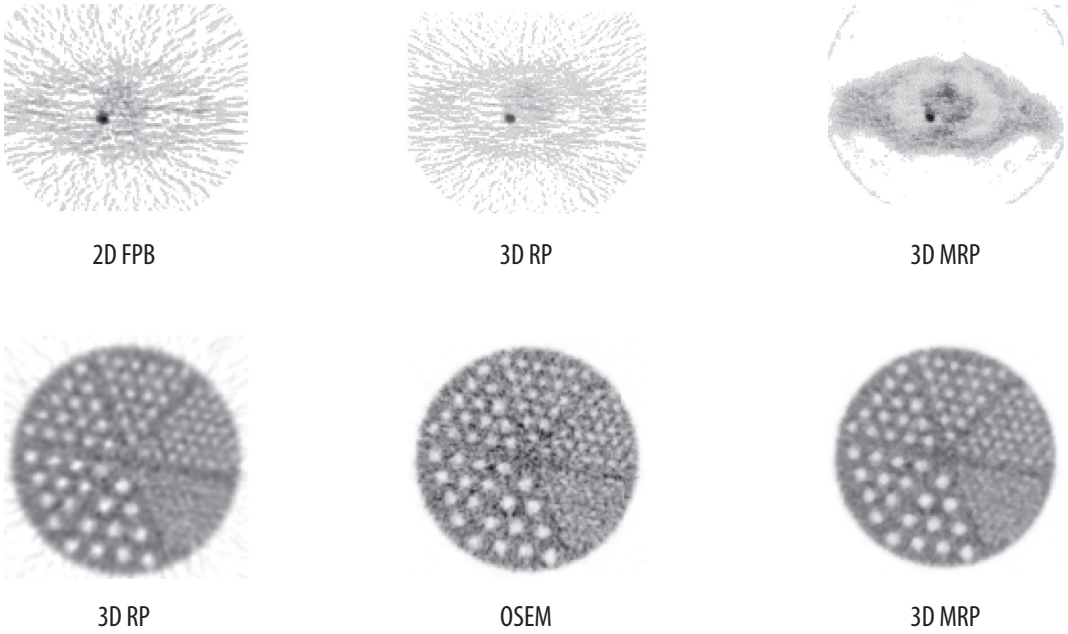
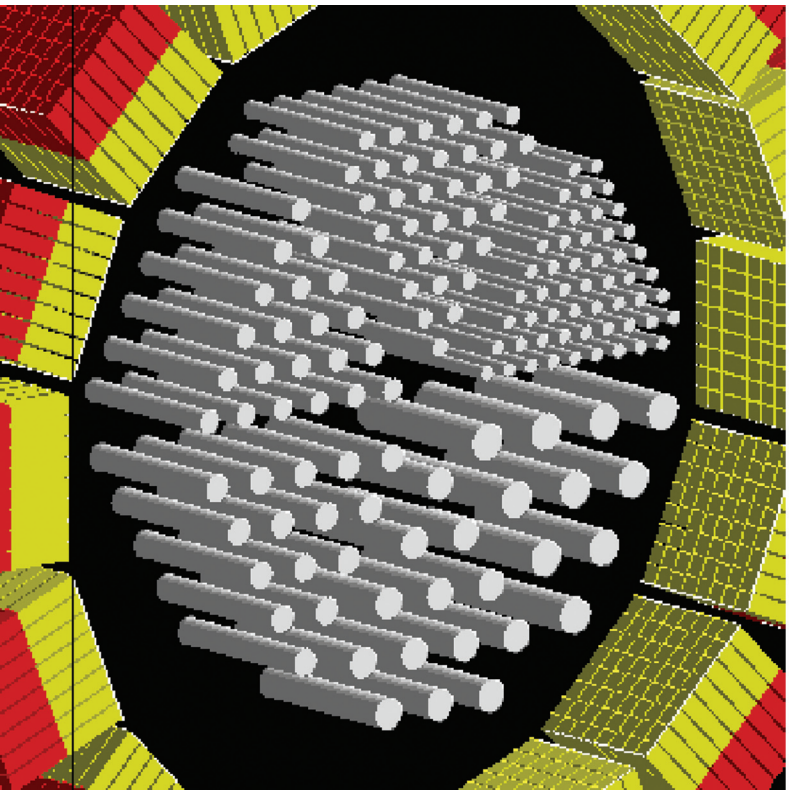


Fig-A13
Different iterative and analytical reconstruction methods
(PARAPET European project)

Until recently, tomographic reconstructions in clinical routine only used analytical methods because they are usually faster and they have interesting properties, for instance in terms of linearity, which makes image understanding and characterisation easier. To quote only a few examples of exact or approximated analytical algorithms, let us mention filtered back projection (FBP), the 3D reprojection algorithm (3DRP) developed for 3D PET reconstruction, the Fourier rebinning algorithm (FORE), which relies on the properties of 3D sinograms in Fourier space, or the Feldkamp algorithm (FDK) for tomographic reconstruction from cone projections. Nevertheless, analytical algorithms have a few flaws: the main one is the bad quality of images with low measurement statistics, where star artefacts resulting from backprojection on highly noised projections appear. Besides, these methods require strict constraints on the geometry of detectors, which absolutely have to cover all the azimuth projection angles around the patient.

In this regard, algorithms based on a phenomenological approach are less demanding and, above all, they make it possible to simulate the reconstruction of data with low counting statistics. These methods iterate a process aiming at optimising an objective function, for instance the likelihood function coming from the Poissonian nature of the data recorded by the tomograph. In this field, let us mention the maximum likelihood expectation maximization (MLEM) algorithm and its variant using ordered subsets (OSEM). Bayes' theorem can also be used in order to introduce a priori information into the image to be reconstructed. In this case, the objective function is penalised by a constraint determined by a wanted property of the image to be reconstructed. This constraint may for instance take the expression of a Gibbs distribution involving a canonical—in the statistical mechanics sense—description of the image's pixels. An important consequence of the iteration process is that it needs high calculation power. Fortunately, with the development of the grid, huge calculation resources massively distributed in this aim are likely to appear. Yet, it has to be noted that it is more difficult to predict the result of an iterative process than the result of an analytical one, and that Monte Carlo simulation is very often a key element to study and optimise this kind of approach.

It finally has to be noted that a tomographic reconstruction library, STIR (Software for Tomographic Image Reconstruction), is available on the Internet: http://stir.irsl.org. This library is the fruit of two successive European projects dedicated to tomographic recontruction for PET: HARMONY and PARAPET. STIR is written in C++ and benefits from the modularity of object-oriented technology. It allows both analytical and phenomenological approaches (Fig-A14).



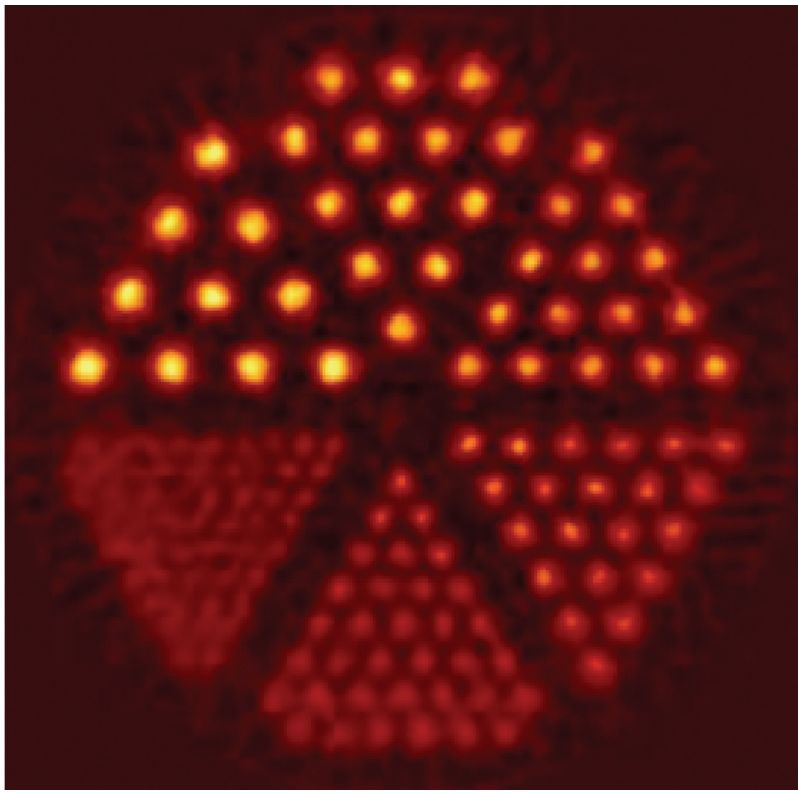


Fig-A14
Simulation and reconstruction of a Derenzo mini-phantom in the ClearPET® using GATE (Crystal Clear, UNIL)

5- Existing infrastructures in Europe

5-1 Isolated initiatives

At the national or European level, many academic research organisations willing to exploit their scientific and technical findings got involved, either a long time ago or more recently, in technological transfer politics. These politics have often focused on the medical field because of the increasing influence of new technologies in medical practice (clinic or research) and because of its positive image in the larger public, which increasingly needs to be informed of the spin-off of fundamental research on society.

Industry, on the other hand, responds to ever-increasing competition by focalising on mid-term research investments, and they find it increasingly difficult to deal with emerging technologies without outside help. To explore the potentialities of future new fields, they would rather rely on public-private partnerships as and when the need arises.

Isolated initiatives are therefore being developed: most of the time they take the form of research contracts or consultancy, involving small, sometimes understaffed, extremely specialised teams, or even individual experts, and they focus on narrow technical fields. As a result, efforts are often scattered: two teams may be working on the same subject, and the small size of scientific teams often limits results. What is more, there is almost no evaluation, coordination or targeting of these activities at a higher level.

5-2 National efforts for concentration: the French example

5-2-1 Instrumentation

Since 2000, activities bordering between physics, biology and medicine have expanded inside IN2P3 and DAPNIA. Indeed, these last few years, laboratories and researchers have strongly committed themselves to this field, while research topics were being progressively organized.

IN2P3 and DAPNIA hold all the winning cards to develop a good interface with biology and medicine. This obviously has to do with their competence in instrumentation, simulation and electronics and with the efficiency of their technical services: all these assets favour the development of original and innovative tools for Life sciences. Progress in medical imaging, for instance, mostly comes from instrumental improvements in subatomic physics and from the new components developed for large-scale projects in this field.

The research teams of a dozen of IN2P3 and DAPNIA laboratories have now gotten together and asked for the creation of a Research Group who would mainly work on the development of new methodological approaches in biomedical imaging.

Imaging mostly focuses on issues linked with therapy and diagnostic imaging, concerning the most frequent pathologies: cancer and cardiovascular and neurological diseases. Early detection, in particular in the field of cancer, requires considerable progress in medical imaging. The aim is therefore to master medical systems in which imaging tools can be combined to diagnostic and therapeutic tools in order to devise more efficient strategies.

Current medical systems often derive from discoveries in fundamental research in physics, and also from important technological developments. X-ray radiography, for instance, was invented long ago; it is still used, with increasingly efficient tools. MRI, which was developed more recently (1960-80) and is universally and abundantly used, is a good example of a medical application of sciences ranging from fundamental quantum physics to advanced technologies, without forgetting nuclear physics (NMR), molecular physics and condensed matter. Spectacular technological progress in these disciplines no doubt foreshadows significant improvements—in technical elements or even in complete systems—for the new generation of 'medical systems'.

In the four coming years, the aim of this Group is therefore to reinforce and to organize the activities of the DAPNIA and IN2P3 teams which work in fields bordering between physics and life sciences (biology, medicine, radiotherapy), allowing common development projects to emerge. With such organizing action, this activity should be more recognized, notably by departments of life sciences.

Until now, this activity was mainly based on local partnerships with biological and medical structures and/or on European programmes, but there were not enough national structures to support it. The Group will encourage collaboration with partners in the field of Life sciences, so as to define collectively the priorities in terms of imaging (other departments in CNRS, INSERM, CEA/DRT and DSV. . .). It should also provide a forum for all the young researchers in the field, especially PhD students.

The agenda relies on the competences of teams already working in the field, and it will revolve around three main themes:

1-Imaging in medicine (diagnosis and therapy)

This theme gathers current research on diagnostic and therapeutic imaging: PET imaging (optimizing electronics and evolving toward whole-body machines), multi-modal imaging (PET-CT or SPECT-CT combinations to associate functional tomographic imaging and anatomical imaging), PET cameras for on-line dosimetric control in hadrontherapy, scintigraphy (quantitative improvements by the use of reconstruction methods) and per-operative imaging.

2-Imaging in biology (metabolic and morphological imaging)

In this field, developments for *in vitro* imaging cover various scales ranging from animal tissue (radio-imagers for autoradiography) to the cell (gene induction and subcellular localisation through fluorescence imaging after local irradiation).

In vivo imaging, especially small animals imaging, is based on the development of tomographic techniques with high spatial resolution: micro-PET, micro-CT, micro-SPECT, associated with animal models. In this field too, multi-modal imaging combining micro-PET/micro-SPECT/X-ray scanners is being developed. Dynamics in this field has largely relied on the CNRS's interdisciplinary programme on small animal imaging ("Imagerie du Petit Animal"). Finally, developments linked to quantification and to kinetic measurement of the radioisotopes used in functional imaging can be mentioned here.

3-Dosimetry (intrumentation and simulation of radiation-living tissue interaction)

Medical imaging is closely related to therapy, especially in the new approaches in radiotherapy. Dosimetry then has to do with the quality control associated to various radio-proton and hadrontherapy treatments (local 3D dosimetry *in situ*, beam dosimetry, checking of on-line treatments with prompt gamma or ^{11}C production…). On-line dosimetry for interventional radiology can also be mentioned (surgery under X-ray control).

Micro- and nano-dosimetric simulation is the second aspect in this field. In radiotherapy, to improve planimetric techniques, nuclear physics' data are needed—cross-sections, measurement of biological data and calculation—for increasingly complex irradiation modes. The models that are being developed are increasingly integrated and take into account the structure of tissues as well as the various mechanisms of cellular response to irradiation (proximity effect, adaptive response, etc.). Simulation is combined with local irradiation methods through which validation with the cellular approach (irradiation of cultivated cells) and with the molecular approach (irradiation of gas-phase molecules) is possible at various scales.

Improvements in these various fields rely on shared instrumental techniques and on the use of Monte Carlo simulation methods both to design detectors and to describe the response function necessary for innovative techniques in tomographic reconstruction. This also holds true for expertise in radiation-matter interaction, which is a common denominator to and a link between all the teams involved in this field. Know-how in terms of detection instrumentation, fast electronics, acquisition systems, reconstruction algorithmics and medical computer science are key assets for this activity, along with all the methods devised for project supervising and the associated quality control.

5-2-2 Biology: French coordination of research on genetic studies ("génopôle" network)

Since 1998, a network of "génopôles" initiated by the French government, local authorities and the French organization against muscular dystrophies ("Association française contre les myopathies") has been progressively put together. This unique network gathers in a single place academic and private research laboratories, biotechnological firms and high-level teaching departments.

The aim of "génopôles" is to encourage and favour the development of large-scale research in biology and the creation of biotechnological firms so that France can rank well in the international scientific and industrial competition.

5-2-3 Medicine: French coordination on fighting cancer ("cancéropôle" network)

France has launched a large nationwide mobilization plan initiated by President Jacques Chirac on July 14, 2002. On January 16, 2003, Professor Jean-François Mattei, Minister for Health, Family and Disabled People, and Claudie Haigneré, State Secretary for Research and New Technologies, announced to the public the proposals made by the orientation committee on cancer. On March 24, 2003, President Chirac introduced the Cancer Plan, which aims at answering the needs of patients, families and people who take care of people with cancer.

Seven cancer networks ("cancéropôles") have been created in the following regional or inter-regional areas: **Grand-Est (North East of France), Grand Ouest (West of France), Ile de France (Paris region), Nord Ouest (North West of France), Provence-Alpes-Côte D'Azur (South East of France) and Rhône-Alpes (East of France). Their action is coordinated by the National Cancer Institute.**

Research themes revolve around the three axes put forward in the orientations of the national plan against cancer:

1- Biology and functional genomics of cancer

2- Clinical research: diagnosis and therapeutic improvements

3- Epidemiology, social sciences

In terms of instrumentation, animal and human imaging is a key support for such research, as all "cancéropôles" have aptly pointed out. For instance, axis n°2—'developing new diagnosis and prognosis tools associated to the logical development of cancer: implementing original clinical trials to evaluate individualised therapeutic strategies'—perfectly corresponds to Cerimed's goals.

A group of Cerimed partners has submitted a project in this context: 'design and clinical evaluation of a positron detector dedicated to breast imaging'.

5-3 European networks

The facts stated in § A5-1, along with various incentives for valorisation and technology transfers encouraged a number of physicists to get organized and gather in international and pluridisciplinary networks, and to initiate collaborations with biomedical teams so as to apply the technologies developed for particles detectors to medical imaging, to build prototypes, validate them and encourage industry to commercially produce them.

5-3-1 Crystal Clear

This attempt at sharing knowledge was initiated by the Crystal Clear collaboration at CERN, in Geneva. This pluridisciplinary and international collaboration was created in 1990 to answer the needs of High Energy Physics, in particular to create new scintillating crystals, dense and fast. From 1997, it turned to medical applications and was joined by several teams specialised in medical imaging. Besides, a network of contacts and partnerships with teams of biologists and medical doctors in all Europe was established so as to better define the goals of the collaboration and to ensure adequate validation of the technologies developed. It is an academic collaboration whose functioning and intellectual prop-

erty management are ruled by a collaboration agreement. Each participant organism is represented in a management committee whose executive power is delegated to a 6-person committee headed by the collaboration's spokesperson. The results obtained by the collaboration are freely shared by its members at the academic level, but industrial transfers are under the responsibility of the CERN's technology transfer group. Today, the members of the collaboration are:

- CERN, Geneva, Switzerland
- University of Lausanne, Switzerland
- University Claude Bernard, Lyon, France (IPNL et LPCML)
- CREATIS, Lyon, France
- Free University of Brussels, Belgium
- Forschungszentrum Jülich, Germany
- LIP Lisbon, Coimbra and Algarve, Portugal
- Institute for Nuclear Problems, Minsk, Bielaruss
- Institute for Physics Research, Ashtarak, Armenia
- University Sungkyunkwan, Seoul, Korea

A number of invited laboratories also participate in the collaboration's purely academic activity:

- University of Sherbrooke, Canada
- University of Valencia, Spain
- Delft University of Technology, Netherlands
- Copernicus University, Torun, Poland
- CEA Saclay/Dapnia, France

Crystal Clear has also established a partnership network with the following biomedical groups:

- "Animage" platform at "génopôle Rhône-Alpes", France
- "Cancéropôle Rhône-Alpes- Auvergne", France
- "Cancéropôle Provence-Alpes-Côte d'Azur", France
- Department of Oncological Surgery, "Centre Anti-Cancéreux Léon Bérard", Lyon, France
- Department of Pharmacology, University of Gent, Belgium
- Department of Nuclear Medicine, University of Gent, Belgium
- "Département de Médecine Nucléaire", Vrije Universiteit Brussels, Belgium
- Zentrum für Medizin, Jülich, Germany
- Hôpital Garcia Orta, Nuclear Medicine Service, Portugal
- IBEB, University Centre for Biophysics and Medical Engineering, Portugal
- IBILI, University Centre for Medical Imaging, Portugal
- CTNAS, PET Centre, Coimbra, Portugal

It also has to be noted that the Crystal Clear collaboration has signed development contracts with Bogoroditsk Technochemical Plant, a Russian company (CERN/ISTC #2039), with the Institute for Research in Physics in Armenia (CERN/ISTC #A613), and with Photonics Materials Ltd. in Scotland (CERN K929/ETT/EP) to produce the scintillating crystals that have been developed for medical applications.

A license agreement has also been passed with raytest GmbH, a German company (License Agreement CERN/K801/ETT), to commercialise CLearPET®, a small animal PET designed and developed through 5 projects in Europe and in Korea.

Crystal Clear also works in close contact with the following companies:

- CPS/CTI (USA)
- Skyscan (Belgium)
- Johnson & Johnson (Belgian branch)
- Technimede (Portugal)
- Medasys (France)
- EFS Electronique, Givors, France
- Photonics materials (UK)
- Radiation monitoring devices (USA)
- Hamamatsu (Japan)

Crystal Clear's technology relies on scintillating crystals, for which it holds a patent (Fig-A15), on new generation photodetectors such as avalanche photodiodes, on fast, highly integrated acquisition electronics, on computer simulation devices and on reconstruction algorithms.

Besides the small animal PET which has already been mentioned, Crystal Clear is starting a project for the development and validation of a PET approach for mammography in collaboration with the PET centre at Coimbra (Portugal), the teaching hospital at Gent (Belgium) and the "cancéropôle Provence-Alpes-Côte d'Azur" (France).

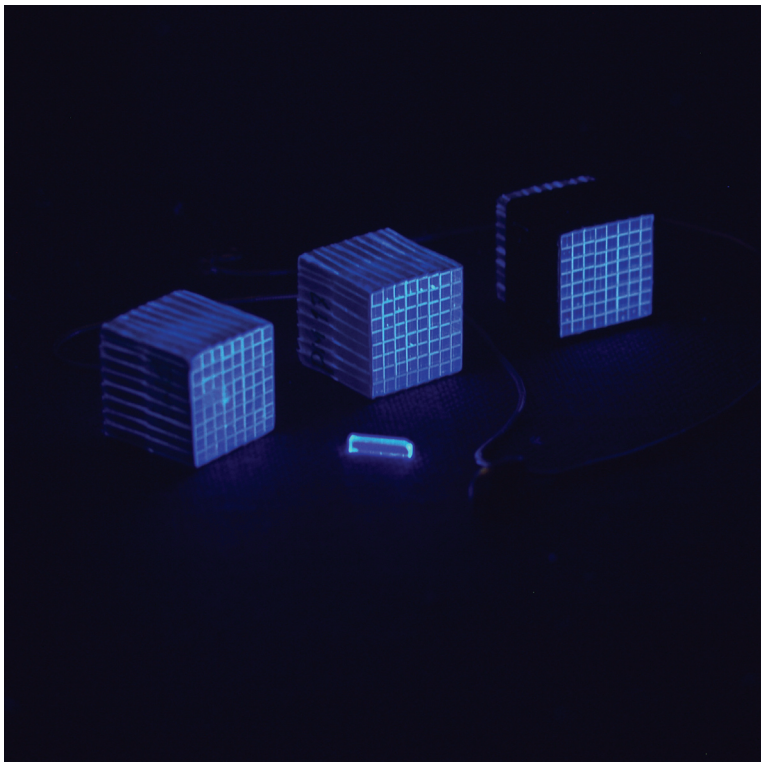


Fig-A15
LSO/LuYAP crystal matrices under UV illumination before their installation in the ClearPET®
(Crystal Clear, CERN)

The collaboration is also putting many efforts in improving the performances of whole-body PET, in collaboration with industry. Some of the new technologies which have been suggested are being introduced experimentally on a high-performance machine, CPS/CTI's HRRT, so as to implement high-resolution study of the human brain, as part of a study aiming at improving PET for oncology.

Among Crystal Clear's main results, we can mention:

- the initialisation and coordination of the OpenGATE collaboration, which developed GATE, a simulation platform for nuclear medicine based on the GEANT4 tools provided by particles physics. This open access platform was officially opened to the public in may 2004 and it has already been used by more than 200 academic and industrial groups all around the world (http://www.opengatecollaboration.org).
- the development, optimisation and setting up, in collaboration with industry, of an industrial production technology in three places—in Russia, Armenia and Scotland—of a new type of scintillating crystals (LuAP and LuYAP), extremely dense, fast, and perfectly fitted for new generation PET (international patent PCT/IB02/02176).
- Building ClearPET®, a small animal PET (Fig-A16 and Fig-A17) that can be adapted for mice and baboons; it is based on innovative technologies—two-crystal phoswich, including LuYAP which provides information about interaction depth, 'free sampling' electronics, etc.—which is now commercialised by raytest GmbH, a German firm (http://www/raytest.de).

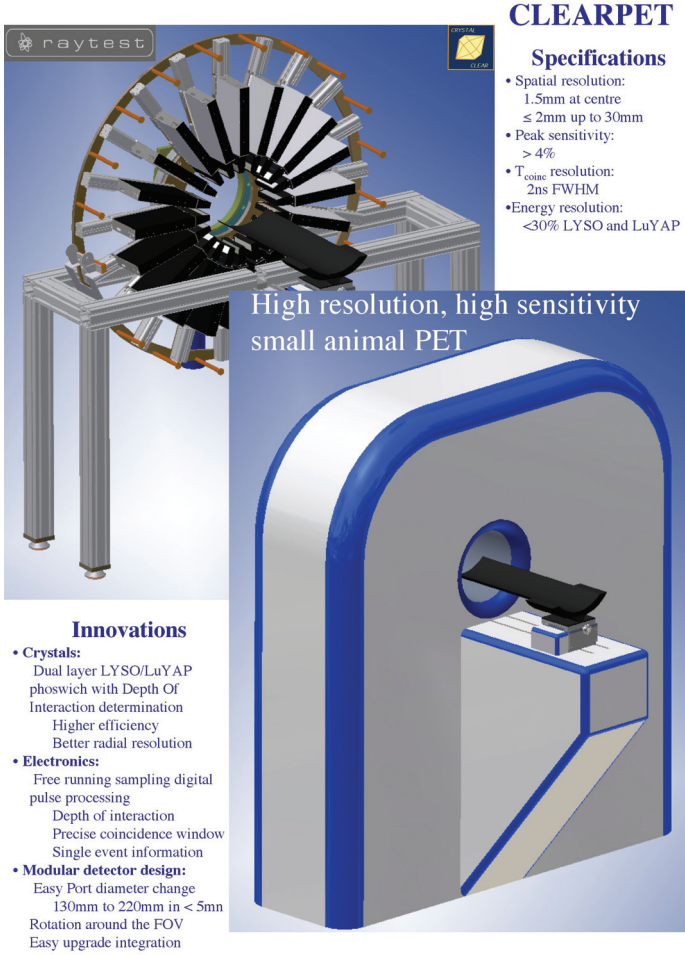
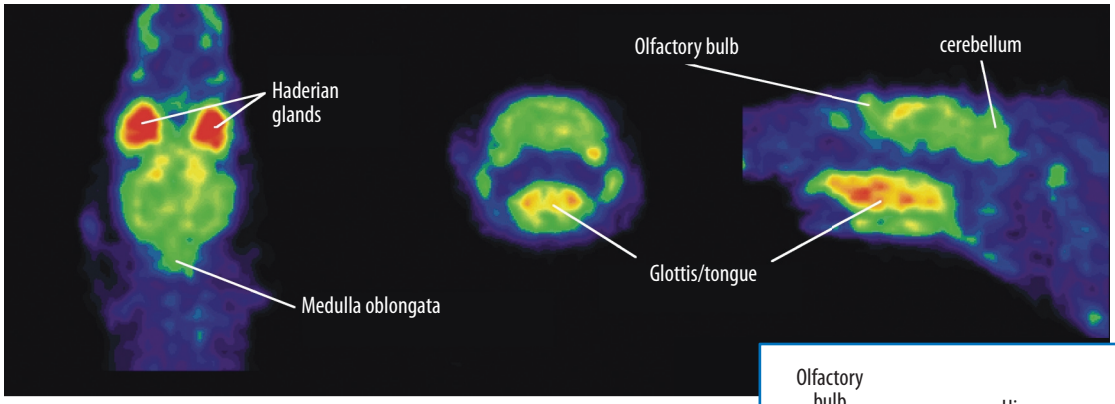


Fig-A16
The ClearPET®



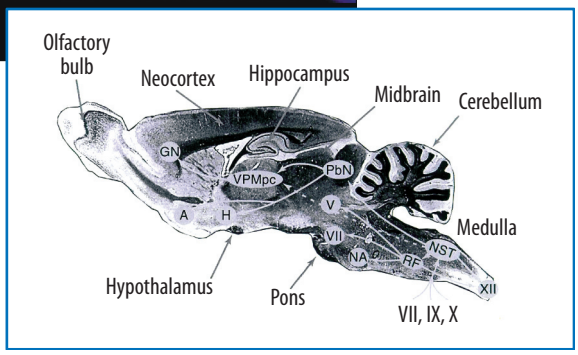


Fig-A17
FDG image of a rat brain with the ClearPET® (Crystal Clear, FZJ)

5-3-2 EuroMedIm

CERN relied on the dynamics of pluridisciplinary resource gathering initiated by Crystal Clear in the field of PET imaging and decided to submit the **EuroMedIm** project within the framework of the 6th 'programme cadre pour la recherche et le développement' (PCRD, programme for research and development). Proposal n° 5299 for an excellence network was submitted within the LIFESCIHEALTH programme under the following heading:

Integration of R&D, prototyping and clinical validation to develop innovative multimodal molecular imaging devices for non-invasive methods in diagnostics and therapeutic monitoring of major diseases.

After evaluation by the experts committee, this proposal ranked second and the project will probably not be funded by Brussels, but the network now exists and has considerably strengthened and widened Crystal Clear's activities.

The main participants are:

In the medical field:

- GEIE-link: European Economic Interest Group—network for cancer. Its members include, in particular, the Centre anticancéreux Léon Bérard in Lyon, the Institut Curie and the Institut Gustave Roussy.
- Deutsche Krebsforschungszentrum (DKFZ) DE Heidelberg
- University and PET centre of Manchester
- Karolinska Institute (Stockholm)
- Université Claude Bernard (Lyon)

In the technical field:

- CERN, Europe
- CEA, France
- CNRS-IN2P3, France
- Free Univsersity, Brussels, Belgium
- Forschungszentrum Jülich GmbH,Allemagne(FZJ)
- Laboratório de Instrumentação e Física Experimental de Partículas, Portugal (LIP)
- Universita di Pisa, Italie
- Soltan Institute of Nuclear Studies, Pologne (SINS)

In the industrial field:

- Real Time Radiography (Israel)
- raytest GmbH (Germany)
- Photonics Materials Ltd. (UK)
- Mirada Solutions Ltd. (UK)
- Ideas ASA (Norway)

One of the aims of this project is to participate to the creation of a **European centre of excellence for molecular and multimodal imaging**, where the technical and medical competences necessary to develop these imaging techniques would be gathered, in close partnership with industry. A training structure should be included, in close partnership with universities and colleges of engineering on the one hand, and with industry on the other hand, so as to train skilled staff for the use and further developments of this equipment. The fact that Brussels did not fund the project in the short term although they pointed to its scientific interest does not jeopardize this aspect, which is included in the Cerimed programme.

5-3-3 Medical networks and European firms working in the field of imaging

EANM

European researchers in nuclear medicine gathered to create a nuclear medicine society: the European Association of Nuclear Medicine (EANM). Its goals are:

- to advance science and education in nuclear medicine for the benefit of public health;
- to promote and co-ordinate, throughout Europe and beyond, discussion and exchange of ideas and results relating to the diagnosis, treatment, research and prevention of diseases through the use of unsealed radioactive substances and the properties of stable nuclides in medicine;
- to provide a suitable medium for the dissemination and discussion of the latest results in the field of nuclear medicine and related subjects.

The EANM was founded in 1985 as the result of a merger between the Society of Nuclear Medicine Europe and the European Nuclear Medicine Society. The merging of the two societies is still reflected within the EANM, as the association simultaneously acts as a forum for individual members and as an 'umbrella' for the nuclear medicine societies of Europe (which convene at the Delegates' Assembly).

The EANM is a professional non-profit medical association based in Vienna (Austria). Membership now exceeds 3,000 and comprises physicians, scientists, technologists and other persons working in nuclear medicine or related fields.

OECI

The Organisation of European Cancer Institutes (OECI) is a non-government, non-profit organization founded in Vienna in 1979. It is now based in Geneva. Its primary objectives are to improve communication and to increase collaborative activities among European cancer institutes, to promote and strengthen comprehensive cancer centres in Europe so as to reduce cancer incidence and mortality and to support cancer patients. Three priorities have been defined:

1- Accrediting cancer centres

2- Transversal research

3- Guidelines for good clinical practice

6- The industrial context

6-1 Current market state and projections[1]

The medical imaging market was estimated at **$14 billion in 2002, with an $18 billion projection for 2007.** This includes imaging equipment, which represents about 75% of this sector, and associated products, which represent the remaining 25%. This field is changing rapidly, because of many factors: spectacular progress in the generic technologies used in imaging systems, competition between the various imaging modalities, the evolution of demand with, in particular, the rise of new therapeutic approaches linked to improvements in molecular biology and to human genome sequencing. All these factors, combined with the constant adaptation of health policies to meet existing needs, but also, in a way, to meet the expectations of the general public, contribute to a rapid evolution of the situation. Thus the various people and institutions involved in the field of imaging must react to the changing situation. In addition, the field of imaging and the pharmaceutical industry are getting increasingly involved with each other, largely due to the advances in molecular imaging.

Mergers, acquisitions and the appearance of numerous niche markets, demonstrate that the market is buoyant and ever-changing. The two most recent important events were GE Healthcare's acquisition of pharmaceutical giant Amersham in 2004 and the acquisition of CPS and CTI by Siemens Medical Solutions in 2005.

X-ray imaging represents the largest part of the imaging market (**$4.5 billion** in 2002), followed by ultrasound imaging ($3 billion). In 2002, nuclear medicine was worth only $1 billion but its evolution rate was by far the highest (30% each year) since in 2005 it was worth $2 billion. In terms of growth, the second best sector is PACS (Picture Archiving and Communication Systems), with a yearly growth rate of 15%. The distribution between the various sectors is presented below (data from 2002, Fig-A18).

1 Data from: CEA/BEM-2002

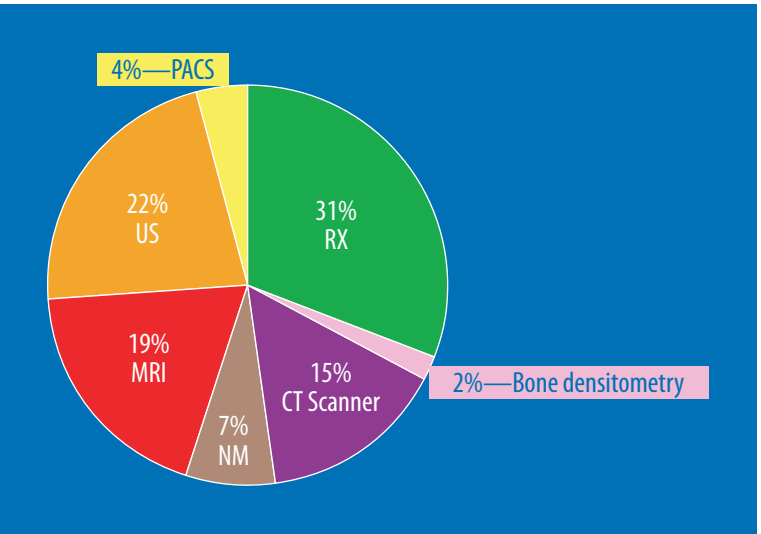


Fig-A18
Distribution of the different imaging market segments
(Courtesy of CEA)

This market has also to be analysed in terms of volume, that is, by looking at the number of units installed and/or at the number of examinations performed each year, because as the selling prices are quite different, the values provide only a partial account of the situation.

- **The most numerous examinations** are by far **X-ray examinations**: about **70%,** or more than 400 million each year, compared with only 25 million each year for nuclear medicine worldwide. The number of X-ray examinations tends to be static, or even to decrease, replaced, among others , by nuclear imaging. The latter increased significantly for the first time when Medicare agreed to reimburse for oncology PET exams, immediately followed by private insurance companies. Another significant increase occurred in 2001 when combined PET-CT scanners were launched: a single exam provides a whole-body image, both anatomical and functional, of the patient. Nuclear medicine could gain still more volume if the use of PET imaging was authorized in the detection and follow-up of neurodegenerative diseases as is already the case for Alzheimer disease in the US.
- **Ultrasound equipment is the most widely sold**—about 25,000 in 2002, mainly used in obstetrics because it is the safest for the patient. X-ray scanners rank second, far ahead of more costly and specific systems like MRI (1000 to 1200 each year), CT-scanners (3.000 to 3.500 each year) or PET (about 150/year), but their number is quickly growing. All these data go back to 2002, but it has to be noted that more than 400 PET-CT were sold in 2004, most of them being in fact multimodal PET-CT scanners. Today (mid-2005) there are over 1000` PET-CT scanners installed in the world.
- In general, equipment is **renewed after 5 to 10 years of use:** the yearly sales rate can therefore be estimated as around 10 to 20% of installed equipment.

The international market **grows around 5 to 6% each year.** It depends a lot on the evolution of healthcare spending, on population ageing, on the increase of life expectancy, and on patients' demand for increasingly early and preventive cures. The growth has been quite regular for the last five years, and should remain the same in the next five years according to most projections.

The **growth rates are quite different for the various modalities**. Today, the sectors with high growth rates are:

- **X-ray with digital detectors:** they should increase by an average of 40% in the next 5 years and should replace some of the conventional X-ray equipment. 5-year estimations for digital X-ray vary from $500 million to $2 billion, but such equipment is still extremely expensive—about $600.000, that is, 3 or 4 times more than traditional equipment in terms of initial investment budget.

- **PET:** still a relatively recent technology, should also increase by an average of 30% in the next 5 years, stimulated by the discovery of new radiopharmaceuticals and by the increasing number of patients with cancers.
- **PACS:** its growth is linked to the development of digital imaging in radiology and of medical information systems, and it should grow at about 20% a year.

The growth of each sector **depends a lot on health policies,** and more specifically on the conditions under which reimbursement occurs after an examination. For instance, the cost of bone densitometry is reimbursed in many countries—Germany, Japan, Spain, Belgium…—but not in France; if in the context of a risk prevention policy its cost was to be reimbursed, bone densitometry should become more widespread in France. Similarly, as the cost of PET has been reimbursed in the United States, it has developed and expanded significantly.

Although in the last 20 years technological revolutions have appeared—CT in the 1970s, MRI in the 1980s, digital X-ray and multi-layer scanners in 1998, PET for oncology in 1998—**no modality has actually disappeared, nor should they in the future,** because each of them brings scientific or technical specificity and/or technico-economic advantages.

Hospitals also increasingly look for an **"overall solution"** provided by one company, as much because they want to rationalise their purchases as because they want equipment to be compatible.

With such conditions—moderate overall growth of about 5% with large differences between the various modalities, significant impact of high-cost technological advances—the strategic stakes for the people and firms working in this field are as follows:

- They need to provide all types of modalities and to develop storage and image analysis software rapidly;
- They have to continue with the development of new technology in collaboration with top research centres;
- They have to grow profitably—in 2000-2001, many small firms were still financially insecure—by winning market share through acquisitions or mergers, as the recent acquisitions and mergers discussed below clearly demonstrate.

6-2 Situation in the world, in Europe and in France

The global distribution of the market of medical imaging has remained constant for the last decade: about 60% in the United States, 30% in Europe and 10% in Japan. It should be noted, however, that Asia has recently but significantly started to emerge; China, in particular, has launched a large-scale national programme.

Geographical distribution only provides average indications for all modalities, as it is quite different for each of them individually. For instance, there are more ultrasound scanners in Europe than in the US. Even in Europe, there are many contrasts between the various modalities. For instance, when the Cancer Plan began in France, there were 10 PET scanners compared with 86 in Germany. The situation is changing rapidly: the Cancer Plan first proposed the purchase of one PET for every billion people; this figure has recently been increased to 75 scanners, that is, one for every 800.000 people. Similarly, 137 new MRI and 183 CT scanners were installed in 2003-2004. Efforts are more or less being made in all European countries—with huge differences between the countries—to make up for the lack of equipment compared to those available in the United States. European X-ray equipment is becoming dated, and Europe is still lagging behind the US in the field of MRI and PET. Overall, the imaging market is present in the so-called "developed" economies and it is dominated by commercial manufacturers from these economies.

Today, the world market is dominated by **three firms which hold more than 75%** of the market: GE Medical Systems (US), Siemens (Germany) and Phillips/Marconi (Netherlands). The rest of the market is held by small companies working in specific technological niches: Hologic (digital detectors), DMS-Appelem (bone densitometry), Aloka (bone densitometry and ultrasound). Today, the "big three" are present in all imaging modalities and fiercely compete for leadership. Some Japanese firms are also present in this sector, even though they remained outside recent mergers/acquisitions: Toshiba ranks 4th, followed by Hitachi, Aloka and Shimadzu.

It has to be noted that in the last decade, the large European companies previously mentioned (Siemens and Phillips) have, for strategic reasons, neglected the sector of nuclear imaging and invested more in CT and MRI. There is almost no small- or medium-scale activity in this sector in France. The promising perspectives opened by genomics and molecular imaging have prompted Phillips and Siemens to recently reconsider their strategy. They are now trying to turn to this neglected sector again, but only through their American subsidies, ADAC for Phillips and CPS/CTI for Siemens. It would be a good thing if Europe was more directly involved in this trend, especially as the competence required in all the necessary areas are available there. This involvement in molecular imaging activities should be developped, and mergers between large imaging groups and pharmaceutical firms—General Electric and Amersham, for instance—suggest that strategies will evolve because of attractive commercial perspectives.

In the last few years there has been **much consolidation** within the field of imaging in general, and more particularly in the sectors associating molecular, genomic and proteomic imaging. In the last few years, there have been some particularly significant mergers:

General Electric Medical (GEM) acquired:

- Lunar (US): bone densitometry
- Magnex (UK): MRI
- Sopha Medical (France): NM (accelerators)
- Kretztechnik (Germany) and Echotech (Germany): ultrasounds
- more recently Imatron (US): EBT scanner (+ Positron in NM)
- Amersham (drugs)

Philips acquired:

- Marconi (US): mainly CT and NM
- ADAC (US): NM and PET
- Agilent (US): ultrasound and PACS.
- HCS (US): ultrasound and HIS

and **Siemens** acquired:

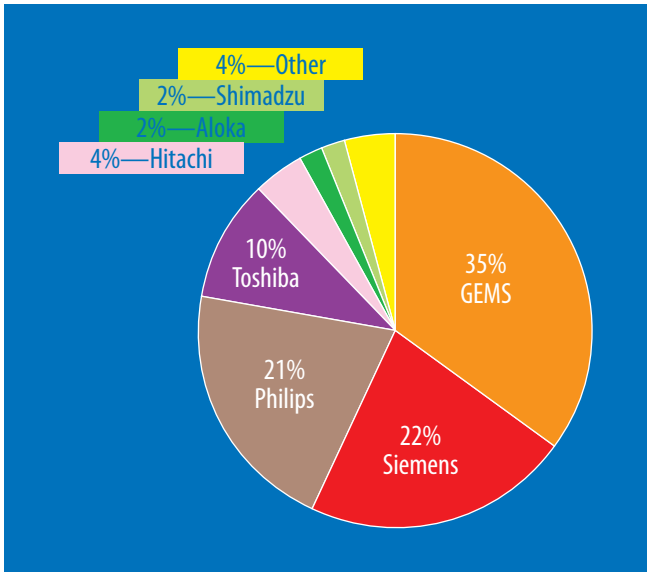
- Acuson (US): ultrasound
- SMS (US): HIS
- CPS (US): PET and PET-CT
- CTI (US): crystals, cyclotrons, radiopharmaceutical production.

Apart from these acquisitions, the market is characterised by **a multitude of agreements and partnerships in the fields of research and development, of OEM or of distribution.** Significant partnerships include Toshiba and Siemens for gamma cameras and PET-CT now with CTI acquisition, Swissray and Marconi for distribution in the US, Hologic and Siemens for distribution in bone densitometry and developments in the field of digital mammography, etc.

GEMS is by far number one on the market with a **total turnover of $7.600 million** in 2002; **Siemens ranks second with $4.700 million and Phillips-Marconi ranks third with $4.500 million.**

GEMS can be described as the leader in CT, MRI and PET, Phillips in ultrasound imaging, and Siemens in X-ray. The market shares of the main firms in the world are visualised on the following graph (Fig-A19, data from 2002).

Fig-A19
Market share between the different imaging industries
(Courtesy of CEA)



France lagged behind in terms of equipment for a long time, but is now making up for this with large-scale projects such as the Cancer Plan. This mainly benefits to the large American companies which dominate the market of imaging, though. The only French-funded company which makes 'whole' imaging systems is DMS-Apelem, a 27 M€ firm with high growth (17%). But imaging equipment is built in France by foreign firms: X-ray and mammography in Buc (GEMS), nuclear medicine (GEMS) ultrasound imaging (Kontron, CharterHouse Group). Large firms also act as providers for imaging firms: Saint Gobain for detectors, Trixell in Moirans or Thales for X-ray tubes.

6-3 Existing partnerships between industry and physics research laboratories

Academic networks involved in activities of technology transfer to medicine, Crystal Clear for instance, have established many industrial relationships, both to meet the needs for generic developments beforehand and to valorise their research afterwards.

For instance, the Crystal Clear collaboration has signed development contracts with Bogoroditsk Technochemical Plant, a Russian company (CERN/ISTC #2039), with the Institute for Research in Physics in Armenia (CERN/ISTC #A613) and with Photonics Materials Ltd. in Scotland (CERN K929/ETT/EP) to produce the scintillating crystals that have been developed for medical applications.

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- Technimede (Portugal)
- Medasys (France)
- EFS Electronique, Givors, France
- Photonics materials (UK)
- Radiation monitoring devices (USA)
- Hamamatsu (Japan)

Generally speaking, to get industrial results for such a technology transfer programme, the needs of users—here, medical doctors and hospital administrators—have to be clearly identified. These needs can be listed under the following 5 headings:

1- **Improving equipment productivity and diminishing imaging costs.** Among other things, shorter examination duration and the capacity to network and store the obtained data are required.

2- **Improving diagnostic precision and early detection of pathology,** a preoccupation which is shared by patients and physicians alike. To achieve this, improved image quality, the capacity to combine modalities, image treatment and sequencing, diagnostics at distance with the help of experts and computer-assisted diagnosis software are required.

3- **Patient comfort and ergonomic equipment.** To achieve this, doses and examination duration have to be reduced, compact equipment which can be brought to the patient has to be devised, and non-invasive methods have to be developed.

4- **Follow-up of therapy efficiency,** which requires image quantification and the possibility of precise screening.

5- Developing tools to **facilitate therapy** and medical and surgical acts. To achieve this, dynamic and interventional imaging have to be developed.

In the last few years, major technological developments have made it possible for commercial companies to respond to these needs, especially in the following fields:

- Development of **digital radiology**, facilitated by the increase in computer memory and image treatment capacity. It provides a quantitative image that can be analysed, sent, and stored and for which film supports are not necessary, thus meeting the need for better productivity, quicker and more precise diagnosis, and shorter examination time. The main applications that were developed in digital radiology are dental radiology, mammography and lung radiology. The result was a growth in PACS software and workstations, the development of computer-assisted diagnosis software and the beginnings of telemedicine under the guise of diagnosis at distance (patients do not have to cover long distances in isolated areas and/or a diagnosis can be confirmed by a specialist).
- **3D modalities:** they appeared in 1998, with multilayer scanners, and they are also used in ultrasound imaging (obstetrics) and MRI. They respond to the need for more precise diagnosis due to better image quality.
- **Fusion of anatomical and functional images:** the main revolution is the fusion of PET and CT in oncology, which makes possible improved and earlier diagnosis, and simulation for radiotherapy and pre-operative planning.

In coming years, a number of technological obstacles will be overcome due to ever closer synergy between all people involved, be they developers or users, and in particular between physicists and imaging companies. These challenges revolve around the latest technological advances, and fall into four categories:

- **'all digital' systems:** there will be further developments in digital radiology; ever more sophisticated and precise computer-assisted diagnosis systems will be developed. Ever more ergonomic and user-friendly workstations shall appear, along with new generations of detectors. Standardised platforms combining all applications will be developed.
- **4D imaging:** after 3D imaging, 4D imaging, also called 'dynamic' imaging, which takes into account the movements of organs—particularly needed in lung and heart imaging—and makes pharmacokinetic studies possible will be developed. This implies intensive work on image acquisition and reconstruction with movement compensation, which in turn implies progress both in algorithms, software and detectors.

The development of 4D imaging will also favour the development of surgical robotics and assisted operations, and of radiotherapy planning. These developments will require close collaboration between diverse fields: computer science, physics and electronics.

- **Molecular imaging:** it appeared at the beginning of the 21st century due to progress in nuclear medicine and in biotechnologies and due to better knowledge about the human genome: the aim is to read the information contained in human cells due to the development of new tracers which can help to detect a pathology even before symptoms appear. As a result, imaging platforms will be miniaturised to make animal exploration possible. These specialised platforms will make it possible to develop new drugs more quickly, but also to make progress in research on new radiopharmaceuticals. Partnerships initiated in 2001 between GEMS, one world leader in imaging, and Smith Kline and Amersham, followed by GEMS's purchase of Amersham in 2004, are ample evidence of this already visible trend. Because of these developments, experts in very diverse fields—biology, physics, electronics, pharmacy—will need to work together.
- **New modalities:** publications on new modalities have appeared recently: optical (infrared: IR spectroscopy of the brain, Imaging Diagnostics Systems's developments on MOPI—Medical Optic Imaging -, laser. . .) and thermal imaging.

There will be new advances in the field of MRI, and new perspectives will open up: higher fields, in vivo spectroscopy. . .

If the fusion of various modalities is still developed in the future, it could lead to fusion within a single device, and therefore a single detector. This is a huge field of investigation which can be explored only with a well-organised large-scale partnership between the public and private research.

B-The Cerimed Programme

1- Goals

1-1 Collecting interdisciplinary competences on the same site

The goal of Cerimed is to promote synergy between various scientific disciplines, so as to develop, in close partnership with industry, a new generation of hig sensitivity molecular imaging systems with excellent spatial and temporal resolution and real multimodal and multifunctional capability. The aim is to obtain in a precise, quick and quantitative way a precise molecular signature of the main diseases, based on non-invasive approaches, to improve their detection, diagnosis and treatment, what would obviously have a significant effect on the human and financial cost of such disease for society. This approach has to be as dynamic and interactive as possible, involving the developers and users of imaging systems, since technological progress opens new possibilities for investigation and research, in particular for medical doctors and biologists, while these possibilities in turn generate further specific needs in terms of instrumentation.

To develop the high-technology instrumentation needed by medical imaging, diverse and complementary expertise is required if a significant contribution is to be made. It should be noted that innovation often emerges at the interface between two or more disciplines. As a result, industry is increasingly investing in mid-term research to the detriment of longer-term research, and must rely on academic research in order to explore future technological possibilities in very different fields that it cannot hope to cover by itself.

Past events have often shown how important it is to collect on the same campus, or at least in the same area, all the competence needed to realise great technological achievements. One can quote the examples of Silicon Valley, of MIT and, closer to us, of MINATEC in Grenoble or of the aeronautic centre in Toulouse. This is exactly what the notion of centre of excellence or "pôle de compétitivité", developed in France in 2005, is about.

Such a perspective has inspired the creation, under the impulsion of Sam Gambhir, of BIOX, a developing centre for molecular imaging based at Stanford University (USA) and supported by the NIH. Cerimed aims at being its European counterpart with a strong additional focus on instrumentation.

In the field of imaging, innovation often comes from physics. Several Nobel Prize Laureates in physics or in physiology and medicine were in fact physicists who were rewarded for discoveries with great impact on medical imaging. To quote only a few examples, Röntgen won the first Nobel prize in physics in 1901 for discovering X rays, Alan McLeod Cormack and Sir Godfrey Newbold Hounsfield won the Nobel Prize in physiology and medicine in 1979 for establishing the base of computer-assisted tomography, and Felix Bloch and Edward Purcell (1952 Nobel prize in physics) and, more recently, Sir Peter Mansfield and Paul C. Lauterbur (2003 Nobel prize in physiology and medicine) were rewarded for their important contributions in the field of nuclear magnetic resonance. Georges Charpak (1992 Nobel prize in physics) must also be mentionned for his invention of the wire chambers, which found many applications in the medical domain.

If the various imaging modalities are based on great principles from nuclear physics, solid-state physics, optics or wave mechanics, implementing complex and highly-integrated imaging systems requires a combination of skills and knowledge in many fields, as was shown in chapter A4. Experts in these fields—material physics, photonics, micro- and nanotechnologies, highly-integrated and low-noise analog electronics, intelligent and fast digital data-acquisition architectures, design of simulation software, of acquisition software for large quantities of data, of image reconstruction and treatment software, of distributed data bases, and finally engineering specialists able to integrate all these systems—have to share their creative skills in a stimulating context where direct contact and exchange are favoured by structures flexible enough to establish dynamic development strategies matching needs that are necessarily ever-changing.

All this must remain closely linked with application—that is, all the people, in medicine and in biology, for whom in-vivo molecular imaging is, or is to become, a crucial investigating tool, in fields as diverse as gene expression, gene therapy, oncology, neurosciences, transgenic animal phenotyping, development of new tracers or new drugs, etc. As the biomedical world is quite different from the world of physics, direct exchanges must be encouraged and young people working at the interface between these two fields have to be trained. This is why, if possible, Cerimed should be established in or near a teaching hospital of European importance.

To summarize, an essential goal of Cerimed is to gather in the same place the various technical competence necessary for the further development of molecular imaging, to encourage collaboration with various scientific and technical institutions (universities, research and training centres, existing European networks, industry) and to incorporate these efforts into a clinical and research environment in biology. Cerimed must be a place where people can work and meet with the participants in the development of molecular imaging in Europe.

1-2 Sharing equipment and methods

One of the advantages of an integrated enough approach of research and development is that equipment and methods can be shared, which favours objective assessment of needs and performances, better incorporation of technological improvements into complex systems and more efficient technology transfer to industry.

Development, integration or validation equipment has to be shared, so that the various participants can have access to equipments which are difficult to obtain or whose duplication or dispersion would be a nonsense in economic terms and would reduce the overall efficiency of the project.

Simulation platforms are a good example of coordination at the appropriate scale. Today, realizations of importance cannot do without sophisticated simulating tools, with which concepts can be validated and performances can be predicted. The trouble is, these tools have to be credible enough, and they too have to have been validated in concrete cases whose analysis is approved of by the whole community. Such was not the case, until recently, in the field of imaging. Industrial machines were based on empirical data, on experience, and on the trial-and-error method. In the last ten years, simulation tools were developed individually by various groups, but there was no coordination effort. As a result, there were many small and not very versatile systems which were hardly taken care of, whose performances were extremely specific to the application for which they were developed, and whose predictions could only remain indicative because there was no large-scale validation which everybody might agree on. The situation changed radically when the GATE (Geant4 Application for Tomographic Emission) platform was launched to answer the need to accommodate complex and flexible scanner geometries based on object language C++, which is recognized by a majority of experts, and on a largely developed code (Geant4) kept up by the particles physics community. Originally created to answer the specific needs of the Crystal Clear collaboration, GATE, which incorporates the Geant4 libraries to a modular, versatile toolbox which can be adapted to nuclear medicine, has been freely accessible as open source since May 2004 (http://www-lphe.epfl.ch/GATE) and has already been downloaded in more than 200 academic institutes and commercial companies in the world.

The same holds true for calculation tools and for data-storing and image-reconstruction and treatment tools, which increasingly have to be designed collectively, relying, in particular, on the concept of 'grid'. These technologies are now being implemented to answer the needs of large-scale calculation in fields like physics or meteorological simulation. They will doubtless influence a more globalised and distributed approach of medical imaging.

Other examples concerning the generic components of this imaging instrumentation could be given. This holds particularly true in the field of electronics. Whatever conversion methods and detector geometries are used, it is imperative to develop sensitive, low-noise amplification circuits and signal-digitization systems with large bandwidth, a high level of integration and low thermal dissipation. Such work requires specific skills and funding that are not necessarily available in all the laboratories which start working in this field. Besides, what is produced can certainly be used for very diverse applications. One of Cerimed's goals is precisely to coordinate such research in various laboratories by helping to define realistic and generic enough goals, by ensuring that some development tools and methods are shared and by suggesting more applications for each of them. It has to be noted that these elements are crucial for efficient technology transfer to industry.

The same holds true of validation systems and protocols. It is certainly not necessary to develop in Europe a large number of technical validation platforms based on 'phantoms' and on operating modes whose diversity would make it difficult to compare results. Developing common protocols and tools with appropriate instrumentation and making them available for the whole community involved in the development of molecular imaging would doubtless be precious and would also contribute to the cohesion of this community.

1-3 Establishing sufficient critical mass

In the last few years, research groups, institutes and organisations of various types have been encouraged to try and valorise their technological developments in the field of imaging. This has been motivated by spectacular improvements in the field of medical imaging, largely covered by the media, by fundamental research's need for a legitimacy linked with society's immediate needs, and by various national and European encouragements for transverse and interdisciplinary projects.

Under its current form, this approach has many flaws. In most cases, although this activity is politically encouraged, it is financially very secondary in laboratories: as a result, it is not granted sufficient funding, and there is no consistent, efficient evaluation system. As a result, efforts are often scattered, there is no overall coordination, and people are often disappointed because there is usually very little practical efficiency. What is more, this kind of research is often hardly credible for companies. As a consequence, there is a 'brain drain' of specialists, who opt for larger structures, in particular the great American universities or medical centres (NIH, Bethesda, Stanford, M. D. Anderson Cancer Centre). Technology transfer to industry is therefore much more dynamic there than it is in Europe. It is significant, for instance, to note that 80% of the researchers working for one of the biggest imaging equipment companies in the United States are Europeans.

To make up for these drawbacks, some coordination efforts were made, with the creation of a few networks like Crystal Clear and EuroMedIm (see § A5). But a much more ambitious action has to be taken in order to increase the critical size of these groups and to better exploit the technological skills available in Europe. In this regard, the examples given in the previous paragraph—simulation platforms and development of efficient and dedicated electronic circuits—are particularly telling, and they can be applied to all the aspects of an interdisciplinary field like molecular imaging. Today, in Europe, there is no recognised centre with imaging as its main field of interest and which could fulfil the following requirements for each technology involved:

- Identify the actual needs in clinic and in biology and define priorities;
- put together the existing competences in Europe so as to meet the technological challenges in the various fields, providing the specialists involved with a common platform and with development and validation tools to complement the input from the institutions they originate from;
- integrate these components in full imaging systems;
- implement large-scale validation processes in realistic and recognised conditions;
- promote industrial development in this field in Europe and develop privileged and large-scale partnerships with the existing firms involved in the field.

One of Cerimed's goals is to achieve sufficient critical mass to meet these requirements, to provide the people and institutions involved in these developments with a focalising point and a forum to share skills and resources. Most of the existing projects, which unfortunately often remain sub-critical for the time being, would thus find a framework where they could be developed with maximum efficiency and productivity.

Hopefully, such coordination and regrouping efforts should lead to increased credibility for current development attempts in the eyes of the organisations who support these activities. As most of the time these activities involve technology transfer from a field to another, the supporting organisations do not have the adequate tools to evaluate, in a field they know nothing about, whether a given proposal—generally involving a small number of people—is valid, or relevant. Integrating such demands into larger projects supported by an interdisciplinary community whose size makes it credible, would make the evaluation of proposals easier, would limit effort dispersal and would thus make it possible to support the really useful and viable projects more efficiently.

Similar arguments hold true for relationships with industry. Details will be given in § B1-5.

1-4 Building and validating technologically advanced prototypes

Cerimed's goal is certainly not to limit individual technology transfer activities already initiated by various research groups, laboratories and institutions in Europe. On the contrary, it aims at encouraging and promoting this kind of initiatives, but also at increasing the teams' critical mass and credibility by providing a consistent and well-structured framework for their activities.

Many generic developments can be decentralised. Cerimed's goal is not to become a centre for technological developments, but a place where the technologies which can be used in molecular imaging can be integrated and validated. Indeed, it is totally unrealistic to think that technologies as different from one another as scintillating crystals, photodetectors, analogical and digital electronics and simulation, acquisition and image reconstruction and treatment software could be validated in complex systems in a completely decentralised way only by the teams who contributed to develop them, with problems in terms of skills and funding.

To answer this need, Cerimed has to bring coherence to all the participants by integrating individual initiatives within a general and coordinated strategy. In this way, new ideas can be generated and new partnerships, and therefore new projects, can be initiated because the laboratories involved will thus have an outlet for all their developments. Generic technologies can be credibly validated only if they are integrated into complete imaging systems, which means that these systems have to be built either from scratch or by transforming and adapting existing equipment so as to integrate the new components.

This would make it possible not only to validate innovative ideas on commercially-oriented instruments, but also to build prototypes which could answer the extremely specific needs—which are not always of immediate industrial interest—expressed by medical doctors and biologists. New research tools would thus become available to them, and it could be shared with groups with insufficient funding to own such equipment.

This is why a centre like Cerimed can consider research lines aiming at designing detectors dedicated to probing specific organs or to research, for instance a positron emission camera for breast or for prostate, a combined PET/MRI scanner for neurosciences, a combined PET/SPECT/CT small animal scanner, etc. Such equipment will not be industrially developed unless it is shown that it is commercially interesting. But it can prove very useful for research, and be a significant asset for the teams who helped to develop it and will therefore be allowed to have access to it. Commercial uses can also result from this research and validation work, and promising perspectives for industrial partnerships can thus be opened. In this regard, positron emission mammography is a good example. It is a known fact that breast cancer detection with classical X-ray mammography is inconclusive in 25% of cases, especially for women with dense tissues or women who underwent plastic or medical surgery. Positron emission imaging's great sensitivity opens promising perspectives for such difficult cases, which concern a large number of people. Serious clinical evaluation of the possibilities offered by this approach, based on a prototype implemented especially for this study, would certainly give impetus to possible commercial exploitation if the conclusions are positive. Commercial companies will not take such action by themselves, but it could be developed within the framework of a public-private partnership involving an academic research and development centre like Cerimed, which can bear alone the risks of reaching a negative conclusion in this kind of studies.

Like large particles detectors, and like most large technological systems, future imaging systems will increasingly need large-scale logistic support to implement and validate complex and highly-integrated prototypes. Nuclear imaging is a case in point, since it implies not only the presence of the instrumentation itself, but also a radioisotope production centre close-by, with a cyclotron and radiochemical installations, all this with security constraints. It has to be noted in passing that with increasingly complex future equipment, this trend is going to grow. The various contributions will increasingly have to be integrated to, and validated in, large and interdisciplinary infrastructures which will remain inaccessible to individual laboratories.

In terms of complex integration, multimodal machines are a typical example. Solving the various constraints resulting from the combination of a PET scanner and a MRI machine is a good example of an important project which most laboratories working in the field of imaging today cannot implement individually. The same holds true of the validation of completely innovative concepts such as Compton cameras, which can only be implemented in a specific and interdisciplinary laboratory.

1-5 Technology transfer to industry

One of the main reasons why the Cerimed centre should be created is that it would contribute to provide Europe with competitive industry in the field of molecular imaging. Large European firms like Siemens and Philips, who neglected nuclear imaging in the last decade, are trying to exploit this segment again, but for the moment they have done so only through their American subsidiaries (CPS, ADAC). Besides, there is almost no small or medium firm working in the field of imaging, although it is rapidly expanding and offers many possibilities to innovate in very diverse activities ranging from generic technologies to their integration to dedicated or whole-body systems, without forgetting the development and distribution of specific radiotracers and, before that, the study and production of specific pharmaceutical drugs. Europe has all the necessary skills at its disposition to become a leader in this field, where it is already excellent at the academic level. Yet, something is missing: an industrially credible, federating unit which could set up and implement efficient technology transfer between research institutions and industry, and thus improve the competitivity loop between discoveries and applications (Fig-B1). This goal is at the core of Cerimed's strategic planning.

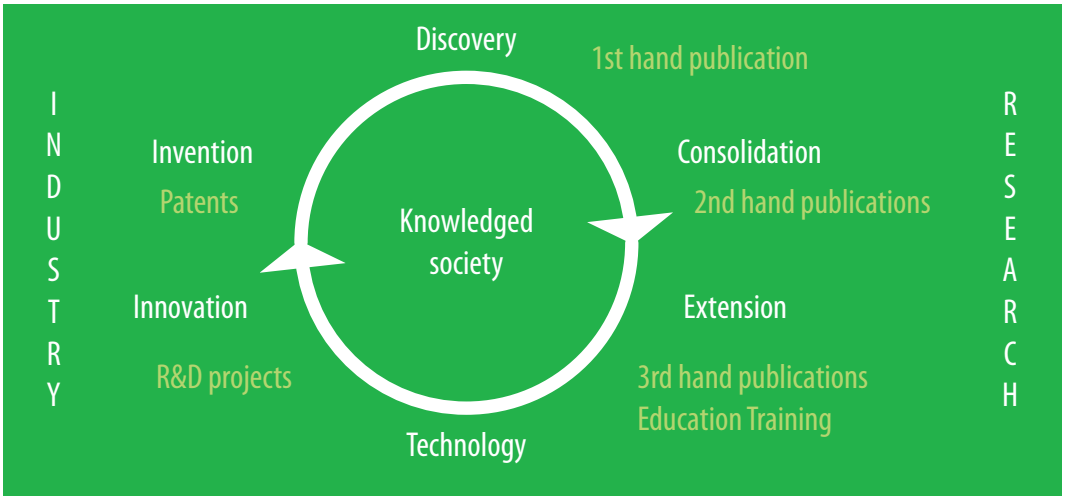


Fig-B1
The competitivity loop
(copyright Vitamib, France)

Cerimed must involve industry in its activities at various levels, coordinating the various development and research strategies, setting up partnerships for limited actions or even for thematic axes, and more generally setting up an efficient organisation for all aspects of technology transfer in the field of molecular imaging. Its part should be to create, at the beginning of its action, a sufficiently organised and credible interface between research laboratories and industry. This implies all that has already been formulated in the previous paragraphs: regrouping and coordinating competences, sharing equipment and methods, achieving sufficient critical size, incorporating innovative ideas into full systems to encourage objective assessment of performances, etc. A recognised centre with physical existence and identifiable structures and people, is essential for commercial companies, who are most of the time at a loss when trying to communicate with networks whose borders are often blurred and whose activity range is often unclear.

Cerimed must first and foremost encourage the setting up of a network involving small and medium firms associated to its research and development activity. This is a high-priority axis with great socio-economic impact. Small and medium firms are more flexible than large firms; they accept to take risks more easily on very specific technological aspects, they can explore niche markets more easily and are therefore indispensable fuel for innovation. The field of application is huge: it goes from the various and numerous generic technologies to building dedicated machines—for small animals, breast, prostate and brain—and to producing and distributing specific tracers. Quick progress in post-genomic research, along with the impact of non-invasive imaging approaches in pharmaceutical research, open up new perspectives in this field.

The involvement of large firms is also of great importance, because they open and organise the market by creating the conditions for economic implication in Europe. It is fundamental to be able to associate this kind of industry at a very early stage of research of development, not only to contribute to acquiring and applying new knowledge, but also to better define strategic goals. Indeed, application-oriented research offers the best possibilities of synergy with industry, especially in the pre-competitive phase, where market constraints are still limited.

2- A centre with 6 departments

Cerimed is an interdisciplinary, federative and transversal European programme which aims at creating a European leadership in the field of molecular imaging by providing an organising structure to combine the numerous skills which already exist in Europe—and especially in PACA—and are at present strongly attracted to the United States, and to create a community of interests in this field for medical doctors, biologists, physicists and icommercial companies. By relying on several existing European networks, the centre wants to provide a convergence point for their efforts, co-ordinating their actions and providing sufficient critical mass and logistics to implement and validate complex and highly integrated prototypes. Strong reliance on generalist educational structures will reinforce its interdisciplinary approach and favour the creation of an industrial network that is currently found sorely lacking in Europe in this field.

In order to reach these ambitious goals with maximum efficiency, Cerimed is organized in 6 departments, which are closely linked in terms of management, so that the people involved and their actions can be co-ordinated in spite of different cultural heritages. The departments cover the following activities:

- Technical development in the field of imaging
- Development and production of new radiotracers
- Definition of goals (diagnosis, therapeutic follow-up and clinical research) and validation in clinic
- Definition of goals and validation in biology (studies on animals)
- Education, training and diffusion of knowledge
- Relationships with industry and industrial valorisation.

2-1 Technological platform

The technological platform has a double aim, but on the whole it must help molecular imaging techniques to progress so as to correspond to specific and clearly-stated needs in clinic and in biological research.

To achieve this goal, it must rely on existing structures and on the individual efforts made in various laboratories in Europe. Cerimed's aim is not to replace them, but, on the contrary, to encourage their action and to favour the integration of all contributions by depending on their complementarity, with clearly-defined goals. These actions therefore have to be identified, the various groups involved have to see one another regularly in meetings, workshops and conferences, and they must be encouraged to set up collaborations, especially to develop generic technologies and to look for new partners who could bring emerging technologies—nanotechnologies, optronics, calculation grids or optical calculators—into the field of molecular imaging. Putting together all these skills and all this knowledge and correctly evaluating the needs and their order of priority will also enable new ideas to emerge and make it possible to identify what needs can realistically be satisfied. This co-ordination role is crucial to set up a real European strategy and to decide what lines of action are the most promising in terms of feasibility and of impact. Such action can be efficiently and credibly taken only by a centre whose primary goal is known to be the development of molecular imaging. At present, such a centre does not exist in Europe.

At another level, Cerimed should create the conditions necessary to a good integration of new technologies or innovative concepts into prototype systems realistic enough to be validated in credible conditions. Assembling these prototypes requires various and diverse skills in different fields: optics, materials, electronics, mechanics, computer science and controls. Adequate infrastructures must be available at Cerimed for each of them. The Cerimed staff in charge of these equipments will have to deal with the integration and assembling of the prototypes in close partnership with the teams who will have contributed to the various technological developments. It will be necessary to host these outside teams so that they can take part in some critical phases of integration and trials on their subsystems.

Consequently, there has to be a mechanics laboratory, various optics, materials and electronics laboratories and sufficient computer infrastructure; all these structures have to be primarily oriented to solve integration issues. Besides, the assembly hall will be large enough and have sufficient equipment, so that three systems of different sizes (scanners dedicated to small animals, breast, brain…) can be simultaneously built, which should correspond to the centre's normal maximum level of activity.

By making this sufficiently equipped and organised platform, which can primarily take care of integration problems in complex medical imaging systems, available for the various instrumentation developers in Europe, Cerimed hopes to stimulate hi-tech technology transfer to this field. Many experts in diverse fields find it difficult to develop their work into specific applications, either because transversal knowledge showing that their work is useful for these applications is lacking, or because they cannot materially demonstrate that usefulness through convincing prototypes.

The example of multimodality shows particularly well that it is necessary to integrate in a consistent, and therefore centralised, way the various contributions on different constituents. The ambitious project of making a really multimodal detector head, which could simultaneously record X- and gamma-rays with different energies, depends as much on the development of innovative concepts in the relevant fields—materials, electronics, signal acquisition and treatment, image reconstruction—as on a good optimisation of the compromises, which will be necessary to integrate all these concepts into a unique and compact system. The technological platform will have to identify and solve this type of problems.

It will also help to validate the technological improvements introduced into prototype systems after their integration. It therefore has to provide appropriate ways and means. The first condition is to create efficient enough simulation tools, so that they can provide credible quantitative data to develop, evaluate and validate new correction, normalisation and reconstruction algorithms. With some of these tools digital phantoms will be created to study performances through simulations, for instance:

- radial, tangential and longitudinal resolutions in reconstructed images
- temporal resolution for certain dynamic processes
- sensitivity profiles for coincidences (PET imaging)
- calculation rates (real, diffused, random events).

In nuclear imaging, the validation methods are also based on the use, in the first phase, of normalised phantoms which represent either calibrated targets or the torso or various organs, and which can be filled with labelled liquids, usually 18F. All the parameters previously mentioned can thus be physically measured, and comparing the results with simulations makes it possible to decide whether knowledge about the detector is correct or not. The methods used to calculate resolution and sensitivity are thus normalised, and the respect of this standardisation guarantees the credibility of the results in the eyes of the international community and of industry.

Providing the necessary support to implement all these methods and to make them available for the various teams who could need to use them is also one of the goals of Cerimed's technological platform.

2-2 Developing and producing radiotracers

The field of application for new nulear imaging devices wholly depends on the development of new radiotracers. To study various organs and their associated pathologies, tracers specific to certain metabolic functions involved in the normal or pathological activity of these organs are needed. As an increasing number of specialised cell and molecular probes have been discovered and implemented, it paves the way, with the use of in vivo imaging methods, to an identification of the transmission channels of biological signals and even maybe to a quantification of genomic expression. It is because scientists found out that FDG was a very sensitive—though not very specific—tracer of cell proliferation that PET imaging became a crucial tool in oncology. Similarly, implementing new tracers associated to dopamine opens promising perspectives for other pathologies like neurodegenerative diseases.

Depending on the radiotracer, PET imaging can evaluate local or absolute blood fluxes, energetic metabolic activity, the synthesis of various proteins, genomic expression, hypoxy and the presence of abnormal proteins (for instance, neurofibrillary plaques). It can also quantify the receptors and mechanisms of membrane transfer in cells. In the last few years, the number of radioactively labelled peptidic molecules for diagnosis and therapeutic applications in oncology has rocketed.

However current imaging equipment's phenotyping possibilities and specificity are hampered by the limited number of available radiotracers and of possibilities to combine them. Using radiotracers rationally, associating them with more efficient imaging equipment, should make it possible soon to envisage molecular profiling of a certain kind of tumours characterized by the over-expression of hormonal receptors—somatostatin, cholecystokinin, gastrin, bombesin—especially in cases of breast or prostate cancer.

In these conditions, the development of new imaging techniques and methodologies cannot be conceived of without parallel, sufficiently wide-ranging action in the field of labellers and radiotracers. The radiotracer department's goal will therefore be not only to ensure that relatively classical radiotracers are produced to meet the needs of local hospitals and of the Cerimed centre—for its trials and for the validation of new generation imaging systems prototypes—, but also to take part in a general effort to develop new products.

As regards this second aspect of its activity, the radiotracer department will first have to assess the situation in France and in Europe, where many groups and networks are already working actively in this field. It is obviously useless to duplicate these efforts in already well-covered fields. In such cases, collaborations or partnerships will be set up so that innovative imaging resources provided by Cerimed and specific tracers developed by these groups can be shared. This approach should be primarily chosen in fields like cognitive sciences, where many people are already working on receptors and neurotransmitters in various places. On the other hand, other fields are much less covered, or only by more individual and limited actions, and in this case, as in the case of what is suggested for imaging technologies, Cerimed could become a rassembling force through the direct contributions it will make in these fields, for instance in oncology.

Of course, the part of the radiotracers production and radiochemical activity destined to supply the instrumentation and experimentation installations associated to Cerimed has to be on the same site as the centre itself, so that it fully belongs to it. Conversely, research and development of new radiotracers in fields covered little or not at all by existing collaborations can be more easily decentralised, to take advantage of large existing structures for instance. In this case, though, the part of these infrastructures' activity which will be dedicated to Cerimed's programme will be structurally dependent on Cerimed, even if it is not geographically close.

2-3 Definition of goals and validation in clinic

The clinical department has two main missions: first, to define precise goals to develop new instruments answering real and clearly identified medical needs, and then validate prototypes built in realistic conditions in accordance with security and ethical procedures.

As for the first mission, the clinical department's part is to provide complete medical view of each development project. As in the case of the technological platform, the local view has to be considered, but a synthesis of the way all the issues at stake in the field of imaging are perceived in various medical centres in Europe also has to be made. The needs thus defined have to be assessed according to the technical possibilities, whose synthesis will be made by the technological platform. This approach will give birth to realistic projects whose progress will be regularly assessed with a view, in particular, not to lose sight of the medical goals, which will remain the ultimate criteria. Thus, regarding all the issues linked to new therapeutic strategies and to the follow-up of patients with cancers, neurodegenerative, genetic or cardiac diseases, to quote only a few examples, the clinical department will assess, in a detailed way, the part that imaging can play in the establishment of new therapeutic targets and in the study of the distribution kinetics and of the mechanisms of action and efficiency of new drugs. Similarly, the need to specifically improve some imaging modalities will be evaluated so that the normal and pathological functions of the brain and of other organs can be probed as aptly as possible; this approach could prove particularly effective in the field of cognitive sciences and of disease prevention.

In all these fields, the clinical platform will set up a precise list of goals, or at least define a level of priority between various parameters like sensitivity, spatial resolution, temporal resolution, compatibility between several modalities, etc. The improvement factor necessary for each parameter will have to be defined as quantitatively as possible in order to meet the requirements of each clinical evaluation. The diagram shown in Fig-B2 gives the example of PET imaging and identifies a number of parameters which will be quantified to answer a series of specific problems. Besides, the whole process has to be dynamic, so as to take into account possible strategic changes resulting from progress or technical difficulties which could not be foreseen or from the evolution of bio-medical demand according to scientific progress in this field.

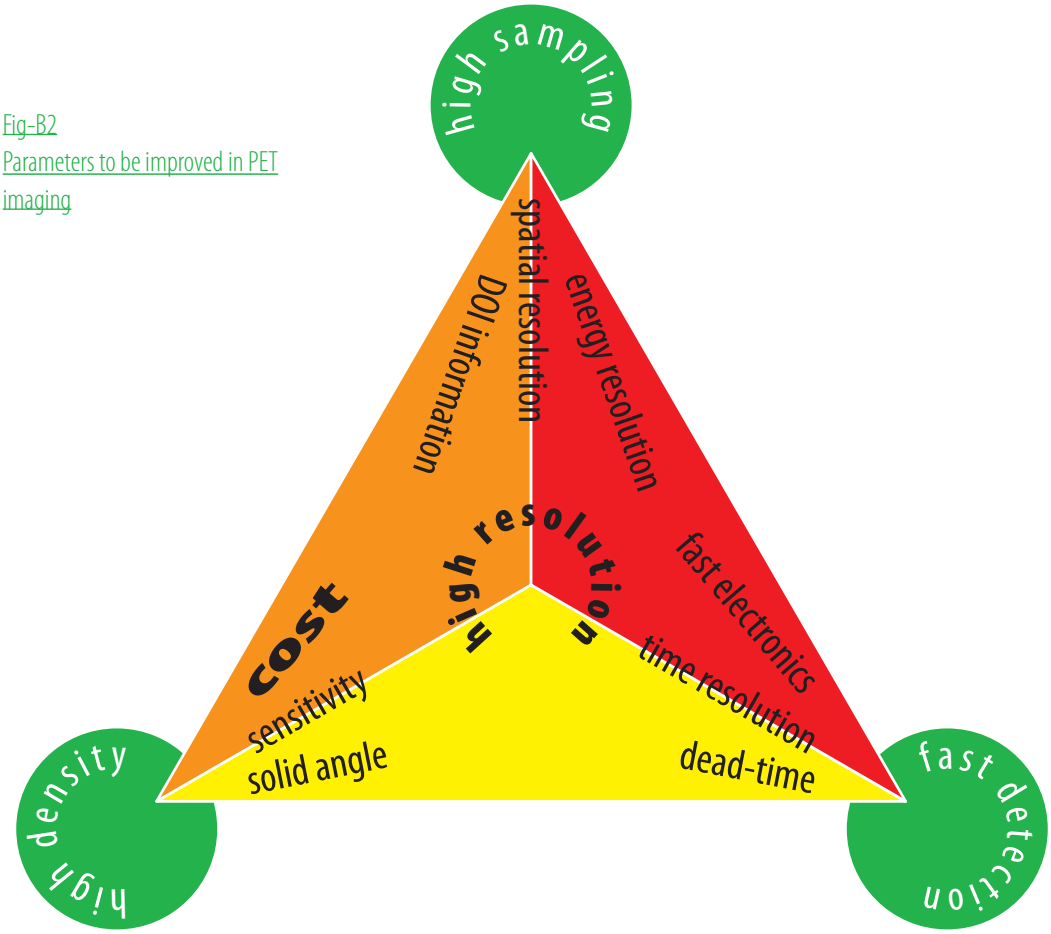


Fig-B2
Parameters to be improved in PET imaging

Once the prototypes have undergone enough technical trials through various physical measurements in laboratories and phantom simulations, validations on animal models or on patients will be implemented, in accordance with extremely strict criteria in terms of hygiene and ethics.

In the clinical field, in particular, a validation committee will be set up; representatives from several important medical centres in France and in Europe will be members of this committee, whose mission will be to define, for each experiment, precise validation protocols compatible with French and European rules and regulations. It will first have to ensure that each project is mature and has been sufficiently technically validated—simulations, phantom trials, possibly animal testing—before allowing clinical trials to be performed. This committee will have to choose the patients and their number,

define the type of examinations to be performed—usually, a comparison between one or several examinations performed on an industrial machine and on a prototype which is being tested—, define comparison criteria and write objective reports, in close partnership with the ethics committees concerned. As far as possible, only patients who already have to undergo classical PET or MRI examinations will be involved, since the aim is first and foremost to assess the potential benefit of new instrumentation compared to existing equipment. If examinations on biological tissues were necessary, they would be performed only on tissues already taken from patients to reach a diagnosis or to establish their therapy planning. In all cases, patients will be duly informed and their consent will be asked for in accordance with usual procedures.

Because of the important technical support set up to make prototypes ready, to ensure that they work during the trials and to guarantee that the environment is favourable to implement the whole validation process, Cerimed has to be set up in a hospital structure, or at least nearby a teaching hospital.

2-4 Definition of goals and validation in biology

Most of the approach described in the previous paragraph also applies to biological studies on animals. It has to be noted that in a number of cases these studies can be considered as a useful stage before the clinical stage. A department specifically dedicated to biological applications is therefore a necessary part of Cerimed.

In this case technological research has to be geared according to the needs of biologists, expressed as precisely as possible for each study. Here again, the perfect equipment does not exist, but by improving certain parameters and by optimising certain technical choices, problems specific to biology can be solved in an efficient and targeted way. The choice of modalities and of their possible combination is also a crucial issue which must not be dissociated from a precise analysis of radiotracers' availability and of future development perspectives in this field. Good synergy with the department in charge of developing and producing specific radiotracers is therefore essential (see § B-2.2).

As for validation processes, the necessary stages will be the same as for human instrumentation, implementing simulation and phantom studies and following strict and well-documented protocols to measure and assess critical parameters, which this validation platform in biology will have to establish, checking that they are followed.

The following stage of the validation process will consist in checking on animals if the performances of prototypes implemented under the supervision of Cerimed really bring the expected benefits compared to standard equipment. The first trials may be quite general, the primary goal being to quantify the main parameters, for instance the profiles on the whole view field of radial, tangential, longitudi-

nal and temporal resolutions, and also sensitivity. Hygiene and ethical rules specific to animal experimentation will have to be respected, and the biology department will have to check that they actually are.

This also implies that a small animal house will have to be created on the very premises of Cerimed so that animals can be housed during the trials in accordance with existing rules and regulations. It has to be noted that setting up Cerimed near existing animal houses large and diversified enough would make this infrastructure much simpler and much less expensive.

The biological studies needing to use new equipment developed for general purposes or for specific cases can then be implemented in various ways. Most of the time, the instruments to be studied will be quite small and their delocalisation into specific biology laboratories should not be a problem, on condition that these laboratories have the necessary infrastructure at their disposal to manage this instrumentation, the associated animal house and the use of radiotracers.

In other cases, sharing the infrastructure will also be a possibility, especially in the case of collaborations between several biology laboratories who do not wish to, or who cannot afford to, buy such instrumentation. In this case, Cerimed could provide a framework to set up such a shared platform, to be used by the biology community. This would bring many practical advantages, and it would certainly make it possible to use less equipment and less staff.

2-5 Education, training, and diffusion of knowledge

Cerimed has two characteristics which make it quite specific:

- it is a transversal programme whose aim is to set up relationships, but also active collaborations between people from extremely diverse scientific disciplines, and with different training and cultural heritages: physicists from various fields (materials, electronics, optics, nuclear physics, signal treatment, etc.), engineers, computer scientists with expertise in simulation software or image reconstruction and treatment, chemists, radiochemists, biologists, medical doctors from various fields (oncology, cardiology, neurology, cognitive sciences, etc.).
- the field of medical imaging, and more particularly of nuclear imaging, is quickly expanding and evolving, and the impact which technological evolution could have in solving certain biomedical problems now or in a close future has been only partially assessed for the moment. There are potential commercial consequences which have to be anticipated, especially as there is almost no existing industrial infrastructure in this field in Europe.

It is therefore crucial, if coherence is to be achieved, if a shared vision around goals perfectly clear for everybody is to be set up and if efficient, dynamic and long-term technology transfer between academic development and research and industry is to be encouraged, to include ambitions in the fields of education and training within the Cerimed programme with a high level of priority.

First, cohesion between the various participants has to be ensured; the condition is a good mutual understanding of the capacities and needs of all communities and of their environment. It is obvious that the motivations and constraints of a researcher who wants to innovate or to understand are different from those of a clinician, who tries to meet patient needs, or those of a commercial company, which has to ensure his production is profitable.

Information therefore has to be constantly exchanged, and work has to be shared on a daily basis. If one excepts technical aspects, Cerimed has to be a place where people can meet and exchange ideas and experiences. This is why, even if Cerimed is an autonomous structure, it should be set up in a teaching hospital, where the Cerimed physicists, engineers, technicians and students, as well as the collaborators from other laboratories, could work in close partnership with medical doctors, biologists and their students. This will have to be taken into account when the centre's architecture is conceived.

The education and training department will have to organise students and researchers exchanges, and to involve industry in these exchanges. Sending students in firms with precise goals and on the basis of projects realised by interdisciplinary collaborations is one of the main vectors of long-term industrial development. Interdisciplinary workshops, seminars on all the technical and biomedical aspects of imaging and mutual training sessions will be regularly organised. To increase Cerimed's international credibility and to turn it into an absolute must in research and development in this field, an international conference will be organised every other year in order to allow all the people working in the field to meet one another. We know from experience that this kind of event is an important source of new ideas and can sow the seeds of new collaborations. EuroMedIm 2006, the first conference of this kind, will be held in Marseille in May 2006. Besides, the larger public will also be informed through public-awareness and information campaigns based on various media (conferences, press articles, web site, open days., etc.).

But long-term strategy and industrial perspectives also have to be taken into account, and they require much deeper work. Appropriate training programmes have to be created or developed in order to train the necessary staff, at the interface between all concerned disciplines. They have to rely on generalist enough curricula, so that engineers-physicists can assimilate the language and the problematics of biologists and medical doctors, and biomedical professionals can integrate more into their approaches the technical aspects of instrumentation and better appreciate the limits and the improving possibilities. One of Cerimed's prominent's goals will be to organise these interface training programmes, relying on the networks of engineering colleges and universities throughout Europe.

2-6 Industrial department

One of the goals of the Cerimed programme is to create the conditions to help Europe to become competitive, and to progressively become a leader in the field of molecular imaging, and in particular in nuclear imaging. For strategic reasons, for many years, large European imaging firms did not invest in this segment, at a time when the field of application of this type of imaging was not clearly defined, but when taking risks would have brought profits. Today, they are finding it difficult to invest in this sector again, and they have done so only through their American subsidiaries. Collaboration between large imaging and pharmaceutical groups (General Electric Amersham, for instance) suggests that important strategic changes resulting from attractive commercial perspectives might take place.

On the other hand, isolated technology transfer activities, supported by some laboratories but only appearing as indirect consequences of other programmes with much higher priority, have been quite disappointing up to now, because of a lack of credibility resulting from insufficient critical size, from an approach not transversal nor interdisciplinary enough, and from structural difficulties to manage intellectual property.

Cerimed's industrial department will establish the indispensable relationships between academic research and development laboratories and commercial companies. The fist condition is to set up a centre which is recognised at a sufficient scale and officially supported by various public authorities at the national and European levels, whose mission is clearly to develop molecular imaging technologies and which can, as a result, appear as a credible partner for industry. Such voluntarist action on the part of the authorities, aiming to gather and co-ordinate efforts which are now extremely scattered, is an indispensable precondition to set up solid partnerships with industry. Large industrial groups will then get involved in these research and development activities more easily. A special cell whose goal will be to establish or reinforce contacts and set up partnerships with industry will be created. Its missions will include:

- informing about and promoting Cerimed's activity,
- organising meetings and workshops on the complementarity between research and development and industrial valorisation in the specific field of molecular imaging,
- identifying common research themes on which constructive complementarity between Cerimed and industry could be based,
- setting up partnership agreements on the axes thus defined,
- managing intellectual property.

At another level, the industrial department also has to help create around Cerimed's premises a business incubator for small and medium firms, start-ups or large groups' subsidiaries acting as bridgeheads, and which will have to work with Cerimed to create some ideas and concepts and to industrially valorise them. Molecular imaging is a recent field and it is evolving very quickly. Not only does it require high-performance technologies whose quick progress open new perspectives every day, but its field of application is also regularly getting wider with the discovery of new biological processes which progressively orient diagnostic and therapeutic strategies to completely innovative directions.

Many commercial opportunities are thus opened in very different niche markets requiring a dynamic and flexible approach, which can only be implemented with the necessary flexibility and reactivity through a close synergy between a research and development centre and a group of small firms. In most cases, young researchers and engineers from Cerimed will provide the inspiration for such industrial activities. Cerimed's industrial department will develop strategies to set up the necessary encouraging measures and to favour permeability between academically-geared Cerimed and its industrial satellites.

To reach this goal, Cerimed will also be able to rely on its education and training department, dispatching or sharing as efficiently as possible physicists (researchers and students), engineers and bio-medical professionals between the Cerimed laboratories and industrial partners. Immediate geographical proximity between Cerimed and these partners therefore seems indispensable.

3- Description of the site

The Cerimed centre has to be organised in such a way as to take into account a number of primary goals on which its legitimacy and its specificity are based:

- It is an interdisciplinary meeting place where physicists, biologists, medical doctors and companies work together to improve molecular imaging. The main part of the activity therefore has to be in the same place, where the best possible synergy between these various communities can be achieved under the recognised label of medical imaging sciences.
- The centre has to maintain close partnerships with all people and institutions involved in developing the generic applications which can applied to imaging, and with a large number of hospitals and biological centres willing to master—rather than endure—their instrumentation. The centre therefore has to be largely open to outside contributions, both from France and from Europe, to facilitate exchanges, to be able to welcome visiting groups and to provide spaces for meetings and exchanges.
- It is an integration centre for complex systems combining various technologies. Sufficient infrastructures in mechanics, electronics and calculation have to be included.
- It is a clinical and animal validation centre: the facilities needed for such experimentation have to be available, in strict accordance with hygiene and ethical regulations. Setting up the centre in or near a teaching hospital is therefore recommended for practical and economic reasons.
- The centre also has to train and educate people, which implies strong reliance on academic structures (universities, schools of engineering). The centre has to be organised so that students can be welcomed and supervised and so that students exchanges can be initiated.
- Partnerships with industry have to be one of the primary goals of the centre. In this regard, setting up the centre near an industrial park would be a great asset.

3-1 Department of Radiopharmaceuticals

Positron Emission Tomography (PET) uses short-lived positron emitters (^{11}C, ^{18}F, ^{15}O, ^{13}N). Positron emitters are produced by irradiating various target materials—gases, liquids, solids—with accelerated particle beams (usually protons or deutons). The beams are produced by a cyclotron which is placed, along with the targets, in a concrete blockhouse with walls whose thickness depends on the nature—energy, presence of a self-shield—of the cyclotron.

The irradiated target materials are transferred to a hot laboratory with lead shield (hot cells and/or lead-shielded boxes). Radiopharmaceuticals are chemically synthesised by automata placed in these shielded enclosures. Quality control on the radiopharmaceuticals is performed in a quality control laboratory.

These precincts constitute a **controlled zone**. For practical reasons, there is also a technical room (for the cyclotron's technical installations) and a control room in the controlled zone. The other rooms, with the ventilation machinery and a room where the gas bottles necessary for the cyclotron can be stored, are outside the controlled zone.

To access the controlled zone, there has to be one entrance and at least one exit door. To go in, people normally use the entrance, which therefore acts as a **safety corridor** and can be used as a changing room. There, a decontamination sink and personal dosimetry intruments (instant dosimetres, hands-and-feet monitor) are also available. A **decontamination shower** is also accessible from the entrance hall.

In the control room, there are the cyclotron's control monitors, radioactivity control equipment, interlock security logics and, possibly, video surveillance for the blockhouse.

The cyclotron is in a concrete **blockhouse**. The thickness of the blockhouse walls depends on what cyclotron is chosen. For a **self-shielded** 10 MeV cyclotron, 30 cm-thick walls satisfy legal prescriptions. For a non-shielded 18 MeV cyclotron, 1.8 to 2 m-thick walls are necessary to adequately protect against neutron and gamma-ray fluence generated when a target is irradiated. To go into the blockhouse, a shielded door with the same protection coefficient against gamma and neutron-rays as the blockhouse's walls is needed.

Inside the **hot laboratory** there are heavy shielded equipment—hot cells and/or shielded boxes—and at least one laboratory chapel equipped to work with isotopes. Outside delivery of liquid radiopharmaceuticals is effected through a safe corridor. If a positron-emitting gas—for instance, $^{15}O_2$—is used, a network of shielded capillary tubes linking the blockhouse directly to the application rooms has to be included.

In **the quality control laboratory**, chemical and radionuclear quality controls are performed. If there is no chemistry laboratory in the radiopharmaceutical-production area, the required equipment—sterilizer, washing-machine, demineralisation equipment, etc.—can be put in the quality control laboratory.

In **the technical room**, the cyclotron's power and control electronics are set up.

The **room** where **gas** bottles are stored has to look onto the outside of the building and there has to be a vent-hole to prevent explosions (hydrogen and fluorine storage).

The technical rooms (monoblock, electric switchboard) are outside the controlled zone. The ventilation installations lead to the building's roof through an independent chimney specific to the controlled zone.

3-2 Technological department

Cerimed is at the crossroads between many generic developments in extremely diverse technological fields on the one hand, and the validation of complex prototypes using these innovative technologies in conditions as realistic as possible from the point of view of biological experimentation and of clinical practice on the other hand. As a result, it is also a meeting place for various disciplines, and it has to encourage innovation. It also has to encourage the creation of a new identity for biomedical physicists, related to better mastery over increasingly complex instrumentation. They are the ones who will be able to initiate authentic dialogue and co-operation with industry.

In the specific context of medicine and biology, most laboratories working on generic developments cannot achieve integration and validation on their own, and, what is more, they often have no legitimacy to do this kind of work.

As a consequence, Cerimed must have a sufficient technical platform at its disposal; this platform should be essentially geared to integration and validation tasks, so that outside teams involved in various projects can work on the site with Cerimed's own staff in good conditions. This platform is designed to answer these needs efficiently, but it also takes into account the availability of some equipment in laboratories working with Cerimed—especially the close-by ones—, which could share it with the centre to meet urgent or specific needs.

3-2-1 Mechanics and material workshop

To assemble and integrate complex prototypes, using components from distributed sources, a material and mechanics workshop is needed. This infrastructure has to be able to play two parts:

- bringing the support necessary to design and implement realistic prototypes integrating contributions from other partner laboratories. This concerns mechanical supports, management of the components' displacements, controls, general services (power supplies, cable routing, cooling systems), the construction of phantoms, etc.
- bringing logistical support to the teams working on assembling and validation. It has to be possible to modify components on demand, to make interface components or to mend a spare part which does not work properly.

This room should be approximately 100 m^2-large; the following components should be available there:

- a CAD monitor
- 2 milling machines with medium capacity, of which one at least should be CNC
- a lathe with medium capacity
- a column drill
- a folding machine
- a bandsaw
- shears for sheet metal
- a welding workstation
- a small metrology room with a marble and measuring tools
- standard hand tools

It has to be noted that this is very classical mechanics workshop equipment, for which the second-hand market is very active.

3-2-2 Electronics laboratory

As in the case of the mechanical workshop, the teams involved in prototype integration and validation projects must have access to a structure where they can perform tests on or adapt the various electronic modules of the machines. This equipment falls into two categories:

- standard material used in all electronics laboratories, including:
  - digital oscilloscopes
  - signal generators
  - various power supplies
  - optoelectronics testing material
  - multimetres
  - soldering workstation
  - etc.

- standardised test benches including, among other things:
  - multichannel acquisition systems
  - FPGA programming and testing systems
  - Coincidence data acquisition bench
  - Spatial and temporal resolution measurement benches.

It should be possible to put all these systems on a surface of approximately 50 m^2.

3-2-3 Computer room

As the last phase of the validation tests relies on the reconstruction and analysis of the images delivered by the prototypes, a computer room should also be available for visitors. The computer modules developed in various laboratories working in partnership with Cerimed have to be available for downloading and for possible corrections or adaptations on the site during the validation phases.

At least 5 workstations will be set up in a room of about 30 m^2 with the following characteristics:

- broadband Internet connection;
- data server (Internet site, scientific calculation libraries, accountancy, human resources, etc.);

- automatic archiving system (automatic archiving of central servers and of personal workstations, CAD stations, etc.);
- processor farm: 256-512 bi-processor knots integrated to the calculation grid for sciences (Monte Carlo simulation, tomographic reconstruction, functional parameter extraction, etc.).

3-2-4 Integration hall

Most on-site activity at Cerimed is geared at assembling complex prototypes often combining several machines in a multimodal approach, and at validating these prototypes. These are the two fields in which Cerimed brings actual added value compared with existing structures, which are much too scattered, and can act as a true federative force at the European level and become a credible partner for industry. Particular attention therefore has to be paid to the establishment of a structure adapted to these activities.

Cerimed must therefore include an assembly and integration hall which can simultaneously accommodate three prototypes. As the time needed for integration and laboratory tests—before animal and clinical experimentation trials—can range from 12 to 24 months depending on the complexity of the system, it is indispensable to plan on a certain amount of overlapping, and to be able to start assembling a prototype while another is being finished and a third one is being tested.

A hall of about 250 m^2 should meet these requirements, with 50 m^2 dedicated to the assembling of each prototype, and the rest to storing equipment and components and to a small dark room which can be used for optical tests and to store light-sensitive-materials.

As a whole, this area's subdivisions have to be adjustable with mobile partition walls so that the various workstations can be at least partly isolated from one another. Besides, the infrastructures classically used for this kind of operations should be available in the hall:

- lifting and handling systems with a capacity of at least 3 tons
- filtered, safe and sufficiently distributed electric power supplies
- broadband Internet connections
- compressed air
- cable distribution system through fake floor or suspended channels.

3-3 Clinical experimentation room

A nuclear medicine unit has to be fit out in accordance with the regulations set by the law ("arrêté du 30 octobre 1981, J. O. du 29 novembre 1981"). The plans have to be approved of by the IRSN/DGSNR (General Bureau for National Safety and Radioprotection) and they have to conform to the instructions of Notice DGSNR/SD9 L/04-V3, whose main rules are listed below.

Establishment and distribution of premises

The premises of a nuclear medicine unit have to be:

- At a distance from general circulations.
- Clearly separated from ordinary premises.
- Built so as to constitute a single unit, thus allowing easy delimitation of a controlled zone.
- Organised according to a hierarchy based on radioactive activities, from the biggest to the smallest

The controlled zone has to include the following rooms:

- Safe entrance and changing-room for the staff, so that working clothes can be separated from ordinary clothes
- Examination and measurement room
- Waiting rooms for injected patients (there have to be distinct rooms for valid patients and for bedridden patients).
- Injection room
- Rooms which have to be immediately near:
- Hot laboratory
- Radioactive waste and effluents storage premises, which can be outside the nuclear medicine unit (basement, outside building…) but have to be classified as part of the controlled zone.

The reception room, secretaries' offices and medical offices normally have to be in the non-controlled zone, except if the distribution of the premises does not make it possible to separate them clearly from the controlled zone.

Establishment of the controlled zone (general characteristics)

- Walls of the hot laboratory and of the injection room: thickness equivalent to 15 cm of ordinary concrete. Walls with no asperity nor corners (rounded angles and edges)
- Flooring (also covering plinths), walls and work surfaces: smooth and waterproof material, with no joint (no tiling) and easily decontaminable.
- Wicket between the hot laboratory and the injection room.
- Sinks cast in one piece with non hand-commanded taps.
- Water plughole on the floor of the hot laboratory and of the injection room.
- Washbasins and showers in the entrance-changing room (on the changing room and work side)
- Washroom reserved for injected patients, joining up to an ordinary septic tank, which is to be directly connected to the building's general collector.

Ventilation of the Controlled Zone (general characteristics)

- Ventilation in depression, independent from the building's general ventilation system, ensuring at least 5 air renewals per hour in the controlled zone.
- Air blowing and extraction vents: set up so as not to create aeraulic perturbations.
- Extraction of tainted air with no recycling hazard:
  - a- End of the air extraction shaft(s): on the roof, sufficiently high (if terrace-roof, the end has to be at least 2 m above terrace level).
  - b- Anti-reflux valve on each extraction shaft if they all join up to a single tube.
- Separate ventilation system for shielded precincts where the radioactive products from the hot laboratory are stored and handled, with independent evacuation shaft equipped with filters.
- Specific ventilation system if radioactive gases are used (Xenon 133…)

Storing Tanks for Radioactive Liquid Effluents (general characteristics)

- Evacuation spot for radioactive liquid effluents, in restricted number inside the nuclear medicine unit, exclusively reserved for such use and signalled accordingly.
- Evacuation pipes for these effluents, connected to a system of two buffer-tanks working alternately in filling mode and in decrease storage mode. These pipes must be for radioactive liquid effluents only.
- Independent, locked, easily accessible room for these buffer-tanks
- Buffer-tanks set up on a safety tank, built with easily decontaminable materials (no concrete), equipped with a level indicator in the nuclear medicine service, with a sampling device in high position and a manhole. The tanking has to include a low point with a liquid leak detector. The level indicator and the leak detector will be checkable from the nuclear medicine service and from the hospital's security headquarters.

Storing Area for Radioactive Waste (general characteristics)

- Covered, fenced and locked area.
- Floor: leak-proof tank, to prevent possible liquid leaks.
- Water supply point, fire extinguisher and electric installations in good condition.

Besides the premises specifically equipped for clinical experimentation, the following material has to be available:

1-To handle Tc99m

- shielded enclosure (6 mm Pb) with an activimetre able to host a Tc99m generator
- if necessary, shielded dry bain-marie and agitator
- 3 lead(ed) bench shields (6 mm Pb), two of which have to be big enough to protect a cage for small rodents (rats, mice).
- 3 shielded 20-litre bins (6 mm Pb)
- 4 shielded protections for needle bins
- shielded syringe-protections (1-ml: 4; 5-ml: 2; 10-ml: 1)
- 1 shielded refrigerator
- 1 shielded storing device (6 mm Pb)
- 1 transport case (for syringes)
- 1 shielded bottle-protector for high activity (more than 100 mCi Tc99m)
- 2 shielded bottle-protectors for medium activity (100 mCi Tc99m)

- 2 shielded bottle-protectors for low activity (10 mCi Tc99m)
- 1 contaminametre
- 1 radiametre

2-To handle 18FDG

- shielded enclosure 45 mm Pb with an activimetre
- 2 lead(ed) bench shields (20 mm Pb), big enough to protect a cage for small rodents (rats, mice).
- 1 shielded semi-automatic injection device
- 1 shielded 20-litre bin (20 mm Pb)
- 1 shielded protection for needle bins
- high-energy, shielded syringe-protections (5-ml: 2; 10-ml: 1)

A possible layout of the clinical experimentation premises which takes all these indications into account is presented in Fig-B3.

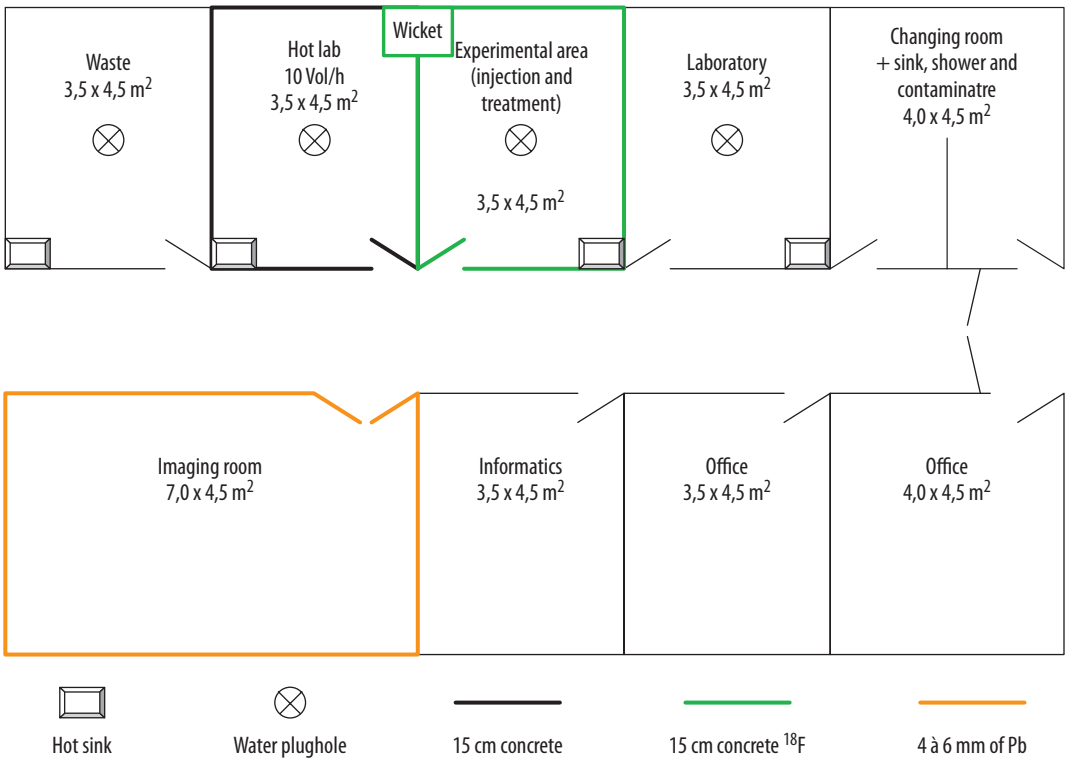


Fig-B3
Clinical experimantation laboratory

3-4 Animal experimentation hall

The aim is to be able to keep animals in an adapted environment from the moment they arrive at Cerimed to the moment they are killed, taking into account animal management and radioactivity. Besides, the use of genetically-modified or xeno-grafted animals, or animals infected with recombining viruses, has to be considered, so that associated biologists can use this laboratory as an imaging platform useful to their projects. But to make it easier to lay out the premises, mice with potentially pathogenic organisms will be excluded. A2 confinement of the area dedicated to animal experimentation seems sufficient. The rooms where radioisotopes will be used or where animals will be experimented upon will need waterproof laminated floor also covering the plinths, smooth and washable walls, impenetrable doors with glass windows on the upper part, upward thresholds impenetrable at door level, depression-ventilated rooms with in and out air-filtering.

Two configurations are possible, depending on the type of experiments to be made. Animal activity on the Cerimed site can be confined to realistic validation of instrumental developments on animal models, and in this case instrumentation will be used for biological studies only on imaging platforms which already exist (ANIMAGE in Lyon) or which are being developed (in Nice, for instance). But researchers may wish to take advantage of Cerimed's infrastructures, and in this case a real imaging platform can be added if there is enough local demand.

Configuration n°1: a minimal structure where animals cannot be housed.

In this first configuration, animals are received individually, images are performed on them and then they can be killed. The premises are then for experimentation, but not for residence. But classifying them as an A2 animal house will make conformity to future legislation possible. A safe corridor has to be used to go in or out of the experimentation zone. In this room, experimenters will be able to put on dedicated over-shoes and jackets. There will also have to be a bench, a threshold, and storage space. This room will have to be the only possible access way for people going into the animal house, which will include rooms with the cameras inside, a room where radioactive solutions will be prepared and a small washing room.

Rather than a single large room, two small rooms will accommodate the experimental cameras, because regulations do not allow two animals to be handled simultaneously in the same room. A room to prepare doses of radioactive solutions, with a space to inject them, is necessary. This room will have to be fitted with a glove box with required protections for radiotracer preparation. It can also be used to store sources. A radiochemical laboratory is indispensable to synthesise some of the molecules. A hood for injections and the equipment necessary to protect experimenters against radiation have to be included. There also has to be protections to handle contaminated animals. There will have to be two rooms to prepare and to store decreasing waste. In the first one—the small washing room—biological and radioactive waste can be sorted and packed, and the cages and supports used for contaminated

animals will be cleaned after having been stored for some time in the storageroom to wait for activity decrease. An autoclave to sterilise biological waste on site is needed. There has to be a freezer in the waste storing room to store dead animals. This room has to be big enough to store the radioisotopes used for gamma imaging, which have longer half-lives than those used for PET imaging. It should be equipped with retention tanks and the required protections. After the isotopes have decreased, all waste will be incinerated.

The experimenter will take his animal, work with the camera and then leave with the empty cage, which will not have to be contaminated. If need be, waiting animal cages will be stored in a small autonomous enclosure. After injection of the radioactive solution, animals will be put in specific cages which will be packed and temporarily stored in a waste storage room. Animals will be allowed to stay only a few hours. At the end of the tests, the animal will be killed and its corpse will be stored in a freezer as long as the activity is higher than allowed.

Configuration n°2: animals will be housed.

In this configuration, animals will be kept in appropriate places before experiments and after injection of the isotopes. It will therefore be possible to do several series of acquisitions on the same animal at different moments. The whole area—except for the waste storing zone—will also be considered as an A2-type animal house, with restricted access through a safety corridor.

Compared with the solution described above, several other rooms will be necessary:

1- At least two rooms to house animals; in each of them, there will be a cage holder, and they will be confined, especially in terms of ventilation and radiation. With two rooms, it will be possible to clean or to decontaminate a room without stopping experiments.

2- A washing room: it will be used, in particular, to clean cages.

3- A food storage room.

4- A room where non-contaminated animals can be kept should be included.

In this configuration, two animal-keepers will have to be recruited.

It will be possible to image animals several times, keeping them alive between acquisitions. Only this configuration will make it possible to observe a biological phenomenon in the same animal as a function of time.

3-5 General services

Cerimed is at the crossroads between numerous and diverse activities. If it meets the need for centralised action in the assembling, testing and animal and clinical validation of complex and highly-integrated imaging systems, it both has to help the numerous generic technologies developed in various institutes and laboratories (in Europe and elsewhere) to converge to the field of imaging on the one hand, and to bring efficient and actual contributions to the field of biomedical applications on the other. From this point of view, it is crucial to work in close partnership with industry.

Cerimed therefore has to have an administrative department which will not only manage the Centre's internal affairs, but will also meet this need for co-ordination. This department will particularly be in charge of the following tasks:

- supporting management of the Cerimed centre: general administration, staff, finances, legal aspects
- setting up project management tools: planning, quality control, financial management
- relationships with parent organizations (national and European)
- relationships with associated laboratories and institutes
- managing intellectual property and relationships with industry
- supporting management of the GIS (groupement d'intérêt scientifique, scientific interest group).

4- Integration of the centre

4-1 Infrastructure

The Cerimed programme requires a building covering an area of 2500 m^2. Surfaces correspond to the various departments in the following way:

Description	m^2
Area for cyclotron 1 + cyclotron 2	300
Radioactive chemistry	200
Offices: cyclotron-radiochemistry (5 people)	50
Administration (10 people)	150
Offices: researchers (10) + students (10)	200
Offices: technical staff (10)	100
Offices: visitors (10)	100
Electronics lab	50
Computer room	50
Mechanics workshop	120
Clean room	50
Materials/optics lab	50
Prototypes assembly hall	250
Animal experimentation hall (with temporary animal house)	150
Clinical experimentation hall (3 large rooms 40 m^2 + 3 small ones (25 m^2)	200
2 meeting rooms (25 seats)	50
Lecture room (100 seats)	100
Storing area	100
Reception, library, common rooms	230
Total	**2500**

Building the centre should approximately cost 7.5 million Euros.

A possible layout is shown on Fig-B4.

The centre's basic equipment cost breakdown is shown below :

Description	K€
Mechanical workshop	500
Electronics lab	400
Computer equipment	100
Mechanical and electronic CAD stations	250
2 cyclotrons + radiochemistry (production and sale)	*5000
X- and gamma-ray sources and system	200
1 high field test magnet	2000
Faraday cage	50
Lab infrastructures	1000
Radioprotection and dosimetry	1000
Animal experimentation infrastructure	250
Animal house infrastructure	250
Furniture	500
Reserve	1000
Total	**15000**

* The cyclotron entry can be divided into two stages. The first one implies one cyclotron and the associated radiochemistry (3 M€).

Fig-B4
The Cerimed facilities

Infrastructure will therefore cost **12 M€ in the first phase** and a total of 15 M€, with a reserve of 1 M€.

4-2 Developing plan for staff and services

The Cerimed centre needs basic staff to both promote and organise the development of molecular imaging (based on the generic work of many laboratories in Europe), and the validation of these technologies through their integration into credible enough prototypes with direct or indirect involvement of concerned laboratories.

Such goals require sufficient technical infrastructures to implement and organise this integration. The mechanics, electronics and calculation laboratories already mentioned will be needed, with the necessary staff to make them work. This staff is estimated around ten technicians/engineers. 5 more people (engineers and technicians) will be needed for the cyclotron and the associated radiochemical platform.

It also seems indispensable, to guarantee group dynamics and to favour cross-fertilization and interconnection between projects, to have a resident team of researchers in physics and medicine. Of course their number will depend on the scale at which the programme is developed, but it can be estimated that there should be at least 15 of them, with possible extension up to 30. Some of these people—but not all of them—can be researchers on secondment from their original laboratories or institutes for long enough periods (at least two years). One of the tasks of this team will be to co-ordinate the activities of Cerimed's six departments.

It will also be necessary to be able to welcome students from medical and scientific universities and from schools of engineering for training periods and theses. Ideally, each scientist among the 10 to 30 mentioned above should be able to supervise a student. Some of the students—but not all of them—could be backed by industry within the framework of specific projects, with a view to training specialised and mobile staff for the future.

Finally, the Centre will need administrative staff in charge of managing the organisational, legal and intellectual property aspects. This department will also be in charge of the relationships with national and European organisations working in partnership with Cerimed. A small team of about ten people should be able to do this work.

On the whole, the centre will initially need 35 people and about ten students, and 55 people and about twenty students once it has started ticking over normally.

4-3 Operating budget

Operating costs fall into three categories:

- Funds needed to recoup the equipment, estimated to 10% of the material each year, and basic overhead expenditure (electricity, services).
- Research budget, about 150K€ for each scientist (physicist or biomedical researcher). An important part of this budget—two thirds—will be invested in European collaborations, especially to finance the assembling and validation of prototypes.
- Wages, 150K€ a year for the technical and administrative staff and 200K€ a year for scientists.

Because Cerimed should progressively grow in terms of technical equipment and of staff, the table below shows the initial and final versions of the operating budget:

Description	Phase 1 K€	Phase 2 K€
Wages (15/30 people @ K€ 200/year)	3000	6000
Wages (20 people @ K€ 150/year)	3000	3000
Research budget (K€ 150/year/researcher)	1500	4500
Equipment recoupment (10%/year)	1000	1500
Overhead expenditure (electricity, services)	500	500
Total	**9000**	**15500**

4-4 Why Set Up Cerimed in France, in the Paca Region?

The project of setting up Cerimed in PACA relies on the competences available in this region in the fields of physics, electronics and optics, of research in biology and of education:

1-Existing competences in physics, electronics and optics

In Marseille

The Centre of particle Physics of Marseille (CPPM), UMR CNRS-"Université de la Méditerranée", which belongs to the National Institute of Nuclear Physics and Particles Physics, (IN2P3). CPPM's director is Dr. Roy Aleksan. The centre has recently recruited an internationally-known professor from Lausanne, Pr. Christian Morel, who designed, within the context of the Crystal Clear network, an efficient small animals PET which will be transfered to CPPM. Pr. Morel will be working in the same area at the CPPM where, in partnership with the Institute of Development Biology of Marseille, (IBDM), Dr. P. Delpierre started last year to design a micro-CT to experiment on mice. 107 people work at the CPPM: 9 teachers-cum-researchers, 26 researchers, 72 engineers and technicians. Two other laboratories on the same campus in Luminy will be able to have some input into the project: the Theoretical Physics Centre, UMR CNRS 6207, University—Director: Pr. Marc Knecht and the Information Sciences and Systems Laboratory, School of engineering of Luminy—Director: Pr. Norbert Giambiasi.

The organisation of the optics and photonics centre of excellence into an association (POP Sud, created in may 2000), followed by the creation of the OPTITEC project, started in 2002 and led to a candidacy for the creation of a french "pôle de compétitivité" with the following title: Photonics: complex optical and imaging systems. Medical imaging, through the Cerimed programme, is part of this "pôle de compétitivité", which provides a clear overall structure, and which has been recently acknowledged by the French Government.

In Nice

The CEA, with the UMR TIRO CEA—University (T. Pourcher and J. Darcourt), where experimental and clinical research projects on the use of NIS (Na+/I- Symporter, an iodine carrier) are developed in SPECT for applications in oncology.

The INRIA (Institut National de recherche en informatique et en automatique, National Institute for Research in Computer science and automatics), which depends on the Ministry for Research and Industry, aims at implementing fundamental and applied research in the field of information and communication sciences and technologies (ICST). It also supervises many technology transfers, paying great attention to training through research, to the spreading of scientific and technical information, to valorisation, to expertise and to involvement in large-scale international programmes. The INRIA, which acts as a federating force for the scientific community working in the field and for industry, massively contributes to developing ICTS in France. With its competences, it can also substantially contribute to the Cerimed programme, especially by developing new image- reconstruction and -filtering strategies.

The laboratories from the PACA region will develop partnerships with other physics laboratories and institutes:

- at the national level with the French laboratories belonging to IN2P3 (National Institute for Particle Physics and Nuclear Physics) and to CEA (French Atomic Energy Commission, materials sciences and life sciences). Besides, Cerimed will set up direct collaborations with various CNRS and industrial laboratories, or with national networks such as MINATEC, involved in the development of various generic technologies which can be useful to imaging.
- At the European level, particularly with national institutions including several particles physics and nuclear physics laboratories associated to the CERN's activities and also involved in technology transfer to medical imaging: INFN in Italy, CIEMAT in Spain, Max Plank in Germany, PPARC in Great Britain, and with many scientific and technological universities.

CERN (European Organization for Nuclear Research), which launched the original concept: Cerimed will benefit from its international federating power and its organising and technical skills. CERN will be able to use Cerimed as an outset for its technology transfer activities in the medical field, especially as up to now direct relationships with industry and with the bio-medical world have not proved very productive. CERN will contribute to the promotion of this European programme among all concerned institutions, especially at the interfaces between physics, medicine, biology and industry. It will encourage those of his researchers who are working on imaging technologies to be in close contact with Cerimed to discuss needs, to generate new ideas and to benefit from recognised validation structures. If need be, it will also help to set up the centre's structural framework, as it did in the past for EMBL and ESO, and it will bring logistical support to the installation of the centre.

The Crystal Clear network is a collaboration initiated by CERN and gathering 17 laboratories (Universities, European Physics institutes) who specialise in the development of new scintillating crystals for various applications, especially for physics and medical imaging detectors. In order to validate its innovative new crystals, Crystal Clear has recently built several prototypes of a small animals PET, ClearPET®, which is now commercialised by the Raytest GmBH company, in Germany, and it will soon build a PET dedicated to breast imaging, ClearPEM®.

2-Existing competences in Clinical Research

They are based on the clinical departments of the AP-HM (Marseille), of the Nice Teaching Hospital, of the Paoli-Calmettes Institute (IPC) and of the Centre Antoine Lacassagne (Nice). The Research Departments and the Clinical Studies Offices of these institutions manage the research projects. The Nuclear Medicine departments of the hospitals and of the cancer centres work with each other in both cities so as to use the PET-CT as efficiently as possible, which shows excellent coordination between the various institutions.

To give an example, in Marseille, clinical research revolves around the Centre for Clinical Investigation, CIC—INSERM, AP-HM and "Université de la Méditerranée". Part of the staff—clinical researchers, state registered nurses, medical doctors specialised in clinical research methodology—is only devoted to realising clinical research protocols. The CIC has sub-departments in each hospital and in the IPC. Before being implemented, all the protocols are validated by a technical committee, which assesses their scientific, ethical and financial relevancy. Competences in clinical research are not limited to oncology, but can also be found in Neurosciences, Cardiology, Metabolic diseases, genetics, etc.—disciplines which will benefit from innovations in medical imaging. Besides, the existence of laboratories like the CRMBM (Centre de Résonance Magnétique Biologique et Médicale, Centre of Biological and Medical Magnetic Resonance) are a significant asset for Cerimed.

Clinical research in oncology is part of the "PACA cancéropôle", whose director is Pr. D. Maraninchi, Professor in the "Université de la Méditerranée", director of the IPC and member of the scientific committee of the National Cancer Institute. This institute co-ordinates the action of the 7 "cancéropôles" created in France and has planned their integration at the European level: research led by Cerimed in oncology will therefore be useful to the whole national and European community in the field. The development of a research line in imaging and of new investigation methods is considered as a primary goal. Clinical research in neurosciences and in diabetology and metabolic diseases is being organised at the national level, with the creation of inter-CIC teams. Cerimed's input to these two research lines will be made easier by these partnerships.

3-Existing competences in biology

In Marseille

Research in biology at the "Université de la Méditerranée" revolves around several federative research institutes (IFR) on three campuses:

- "Médecine Timone" with:
  - The IFR department of human physiopathology
  - The IFR department of transmissible diseases and tropical pathologies
  - The IFR department of brain and cognition sciences
- "Médecine Nord" with
  - IFR Jean Roche, department of cellular interactions
- Luminy (Faculty of sciences) with
  - The IFR department of immunology and oncology
  - The institute of development biology.

On each campus, animal houses—conventional and transgenic—are operational and work in accordance with existing rules and regulations.

21 CNRS laboratories, 19 INSERM laboratories and 23 "Equipes d'accueil" (research teams having signed contracts with the Ministry for Research) belong to these federative institutes. The research lines have to do with 6 of the 11 primary themes defined by the "Université de la Méditerranée": immunology and oncology; genetics and development; microbiology; transmissible pathologies; neurosciences; nutritional, metabolic and cardiovascular physiopathology; environment. The two other universities in Aix-Marseille specialise in other disciplines: Chemistry, Physics, Mathematics, Law, Arts. They have also developed activities in biology, and are then complementary with the "Université de la Méditerranée".

In Nice

The research groups are gathered in IFR 50, 'Genetics and Molecular signalisation' on the one hand, with 12 laboratories under contract with the State—7 INSERM laboratories, 1 CNRS laboratory, 3 'équipes d'accueil' and 1 CEA laboratory—and in the institute of molecular and cell pharmacology, UMR 6097) on the other. They do research in immunology, oncology, nutrition and pharmacology.

There are many interactions between Marseille and Nice: their association in the "cancéropôle-Provence Côte d'Azur and in Marseille-Nice "génopôle" shows it. The two cities often organise common scientific meetings and co-ordinated actions. Local authorities efficiently support the research programmes.

4-Existing competences in training/education (schools of engineering, universities in Aix-Marseille)

Two schools of engineering, the Ecole Généraliste des Ingénieurs de Marseille (EGIM), belonging to the network of "Ecoles Centrales" (national group of schools of engineering), and the "Ecole Supérieure des Ingénieurs de Marseille" (ESIL), as well as the health sector (Faculties of medicine and pharmacy), will train students in this field bordering between physics, biology, medicine and industry. Second-year students at the EGIM started being trained in this field in the academic year 2004-2005. Such studies can lead to doctoral theses within the framework of the doctoral school for life and health sciences, Pr. A. Nieoullon and the doctoral school for physics, (Pr. J.-J. Aubert). Here again, the close links between these schools in PACA and other French and European schools and universities will ficilitate exchanges at the European level.

5- Infrastructure and management

Such a centre needs a specific, supra-institutional status, in order to deal with the European dimension of the programme under direct supervision of the concerned ministry/ies. It would also guarantee the centre's flexibility and independence when co-ordinating contributions from various institutions—CEA, CNRS, INSERM and their European counterparts, and the various hospital networks or private organisations—contributing to certain aspects of its activity. A GIS (scientific interest group) at the European scale, with a convention defining the way each partner should participate, could be the adequate structure. This convention will specify the resources to be developed and the way they must be shared between the various partners, and above all the conditions in which intellectual property is to be managed, the building to be cleaned and maintained, the researchers and teachers-cum-researchers to be welcomed.

At the financial level, it is crucial to put forward the technology transfer—from fields generally supported by public research to industry—involved in the projects implemented under Cerimed's supervision. The aim is really to contribute to shortening the research-to-innovation-to-industry circuit within the context of a health policy at the heart of public preoccupations. Funds from both institutional and private sources seem to be the most adequate financing system for such a complementary programme. These funds from various sources can be managed within the framework of a Public-Private Foundation or of its European counterpart, a European Cooperative Society. The infrastructure—building and associated equipment—and the overhead expenditure might be financed by local authorities and by the State. The staff would include one third of people on secondment from partner institutions, one third of international staff recruited by the State—based on a salary scale in line with international officials' wages -, and one third recruited by the foundation. Local authorities would be asked to contribute to financing grants for students. The projects will be financed by the foundation on the one hand and, via answering various invitations to tender, by national—ANR, "cancéropôles, génopôles", etc.—and European—FP7, CRAFT, NEST, etc.—programmes on the other hand. Some specific projects will also be financed directly by restricted agreements, especially those based on industrial contracts.

In the current transition phase when Cerimed is being set up, a temporary structure has been created. A project leader, **Prof. Charles Oliver,** has been appointed by Prof. Yvon Berland, President of the "Université de la Méditerranée".

C. Oliver heads an executive committee, whose mission consists in deciding what political actions should be taken and how Cerimed should be set up and achieve international influence. Besides its president, who co-ordinates the setting up of the centre, **the committee includes a physicist as Technical Director, P. Lecoq (CERN, Geneva) and a physician as Medical Director, O. Mundler ("Université de la Méditerranée").** The members of the committee are listed below:

- Chairman: C. Oliver ("Université de la Méditerranée")
- Technical Director: P. Lecoq (CERN, Geneva)
- Medical Director: O. Mundler ("Université de la Méditerranée")
- R. Aleksan (CPPM, Marseille)
- V. Atger (Cancéropôle PACA)
- J. Boulesteix ("Observatoire Marseille-Provence", OPTITEC)
- C. Chagnaud (Radiology, "Université de la Méditerranée")
- J. Darcourt (PU-PH, Biophysics and nuclear medicine, Nice)
- J.P. Fabre (EGIM)
- M. Janier (Creatis-CERMEP, Lyon)
- P. Le Du (CEA-DAPNIA, Saclay)
- R. Rieu (ESIL, head of the department of Biomedical engineering)
- S. Tavernier (Vrije Universiteit Brussels, spokesman of the Crystal Clear Collaboration)
- D. Townsend (Univ. of Tennessee, Knoxville, USA)

The Technical director P. Lecoq and the Medical Director O. Mundler head a Projects Committee in charge of defining the scientific content of the Cerimed programme: what main lines of research must be developed, what new technologies must be primarily implemented, with a view to making imaging progress in a way really useful to medical doctors and biologists. The members of this Projects Committee are listed below:

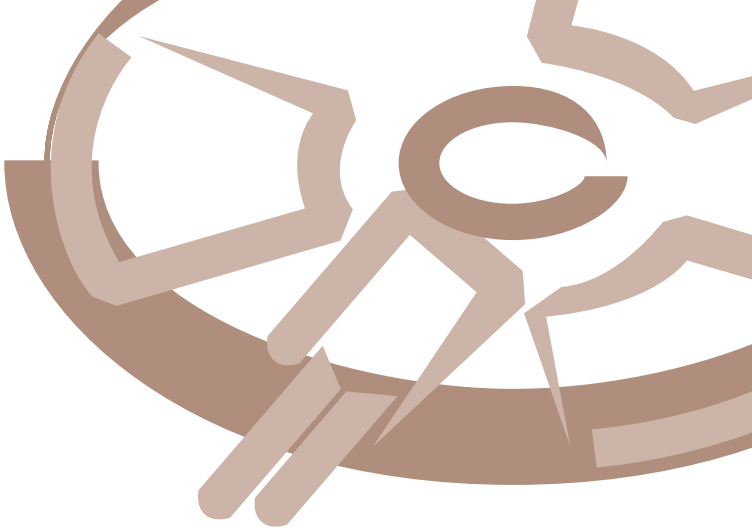
- Co-chairmen: P. Lecoq (Technical director) and O. Mundler (Medical Director)
- Ex-officio member: C. Oliver (chairman of the executive committee)
- L. Bidaut (M. D. Anderson Cancer Center, Houston)
- P. Cozzone (CHU Timone)
- S. Mensah (CNRS, LMA)
- C. Morel (CPPM, Crystal Clear)
- D. Sappey-Marinier (Creatis, Lyons)
- P. Delpierre (CPPM)
- F. Flory (EGIM)
- M. Hofmann (Hopital Insel, Berne)
- P. Mangeot (CEA-DAPNIA, Saclay)
- J. Pailhous (IFR E.J. Marey)
- T. Pourcher (CEA Unité TIRO-Nice).

In the future, Cerimed's structures will have to take into account the interdisciplinary aspect of the programme and the diversity of its financing sources.

A Board of directors will be the highest decision-making instance of the Centre. Its members will be high-level representatives from each institution working in partnership with Cerimed, and they will make decisions on the centre's general policy and on the integration of new members, and make strategic decisions based on recommendations from the Executive Committee and the Scientific Board. The Board of directors will set up the Scientific Board, appoint a Technical Director and a Medical Director to head the Executive Committee and ensure that all involved communities always are fairly and equally represented. It will particularly focus on implementing an adequate strategy for the financial management of the Centre. To answer specific needs, it will have the possibility to set up ad-hoc working group for a given period of time. Finally, it will implement the tools necessary for safety, ethical and confidentiality rules to be respected.

The Scientific Board's members will be independent scientific experts well-known in the various concerned disciplines and chosen by the Board of Directors. The Scientific Board's goal will be to help the Board of Directors to define Cerimed's scientific policy. The experts will be chosen at the international level, ensuring a system of replacement guaranteeing continuity on the one hand and adaptation to the evolution of technologies and needs on the other hand. The Board will select projects according to the input they might bring at more or less long term to biology or clinic, taking into account their technical credibility. It will define follow-up and improvement criteria and suggest a methodology to regularly evaluate the projects' progress. It will more particularly appreciate the moment when evaluations on animals or men can be authorized, the final decision being made by the Board of Directors.

The Executive Committee will be co-headed by a physicist and a medical doctor or a biologist. Its aim will be to implement the policy initiated by the Board of directors. It will implement all the tools necessary for planning, resource management and expenditure control. It will also implement an insurance and quality control policy in the various projects. It will see to the good functioning of each of the 6 departments, ensuring that available resources are fairly distributed and shared. It will arbitrate on the priorities between various projects. It will be in charge of anticipating and identifying unforeseen difficulties—technical, administrative, etc.—and of suggesting solutions to solve them. It will account to the Board of Directors for its actions.



Glossary

APD	Avalanche Photodiode
ASIC	Application Specified Integrated Circuit
BOLD	Blood Oxygenation Dependent contrast
CEA	Atomic Energy Commission, France
CERIMED	European Centre for Research in Medical Imaging (url: www.cern.ch/cerimed) Centre Européen de Recherche en Imagerie Médicale
CERN	European Organization for Nuclear Research, Geneva, Switzerland (url: www.cern.ch)
CMOS	Complementary Metal Oxyde Semiconductor
CMS	Compact Muon Solenoid (one of the LHC experiments at CERN)
CNRS	National Centre for Scientific Research, France
CPPM	Centre of particle physics of Marseille, France
CT	Computer tomography
DAPNIA	CEA Laboratory on Astrophysics, Nuclear Physics, Particle Physics and Associated Detectors, Saclay, France
FDG	2-[^{18}F]fluoro-2-déoxy-D-glucose
FPGA	Field Programmable Gate Array
HPD	Hybrid photodetector
IMRT	Intensity Modulated Radiation Therapy
IN2P3	National Institute of Nuclear Physics and Particles Physics, France
INRIA	National Institute for Research in Computer science and automatics, France
INSERM	National Institute for Health and Medical Research, France

LHC	Large Hadron Collider at CERN
LOR	Line Of Response for two gamma rays in coincidence in PET
MRI	Magnetic Resonance Imaging
NIH	National Institute of Health (USA)
PACS	Picture Archiving and Communication Systems
PET	Positron Emission Tomography
PMT	Photomultiplier tube
SPECT	Single Photon Emission Computed Tomography
SUV	Standart Uptake Value
VLSI	Very Large Scale Integration

http://cerimed.web.cern.ch