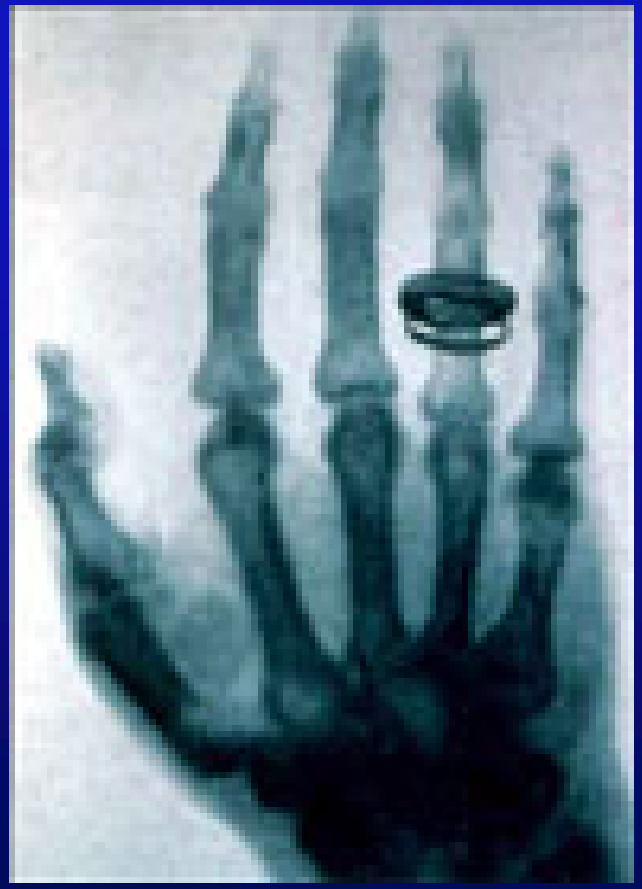
Spin-off from particle detectors in the field of medicine and biology

Paul Lecoq
CERN, Geneva

X-Rays, the fastest technology transfer example



- **On November 8, 1895 Röntgen discovered X-Rays**
- **On November 22, 1895 he takes the first image of his wife's hand**

Röntgen received the first Nobel prize in physics in 1901

Ionizing radiations in cancer therapy

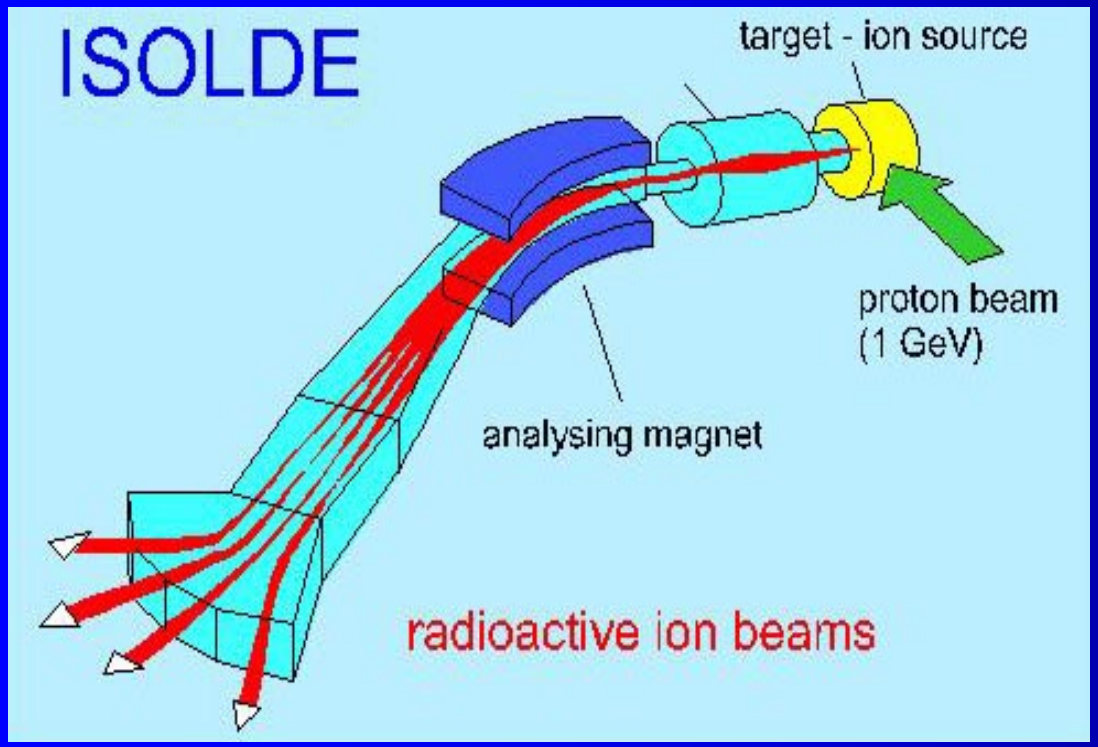
QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

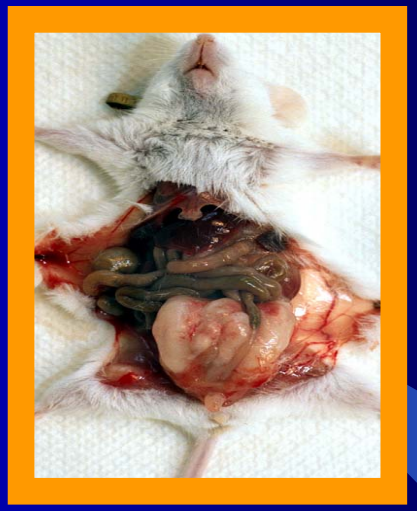
Radioisotopes in therapy

	Gamma knife	ß-knife	α-knife = "systemic hadrontherapy"	Auger knife
ISOTOPE	^{60}Co	^{131}I, ^{90}Y, ^{153}Sm, ^{166}Ho, Others	$^{212, 213}$Bi, ^{211}At, ^{149}Tb, $^{223, 224}$Ra	^{125}I ^{165}Er
	E_g > 1 MeV	$E_ß$ 1 – 3 MeV	E_a 4–8 MeV	E_e few eV
Range	Full body penetration	about 1 cm	30 – 80 µm	1 µm
Application	Head cancer	RIT Radio-immuno therapy	Leukemia metastases	future
	Tissue surgery ex vivo	Tissue surgery in vivo	Cell surgery	Molecular surgery

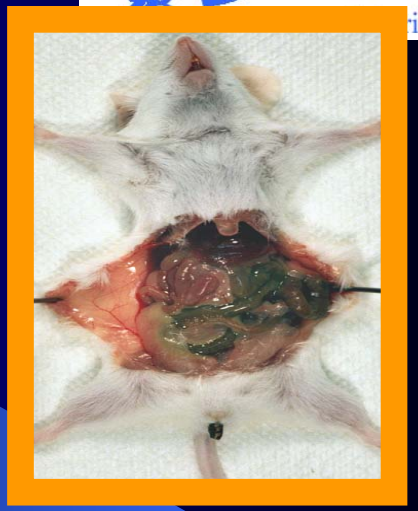
Gerd-Jürgen BEYER

Terbium produced with 1 GeV protons + ISOLDE





Tumor



No tumor after treatment with ^{149}Terbium

Experimental evidence of the usefulness of α- immunoconjugates for micrometastases

ISOLDE and high power (MW) targets (EURISOL) allows the production of novel isotopes

From U. Amaldi

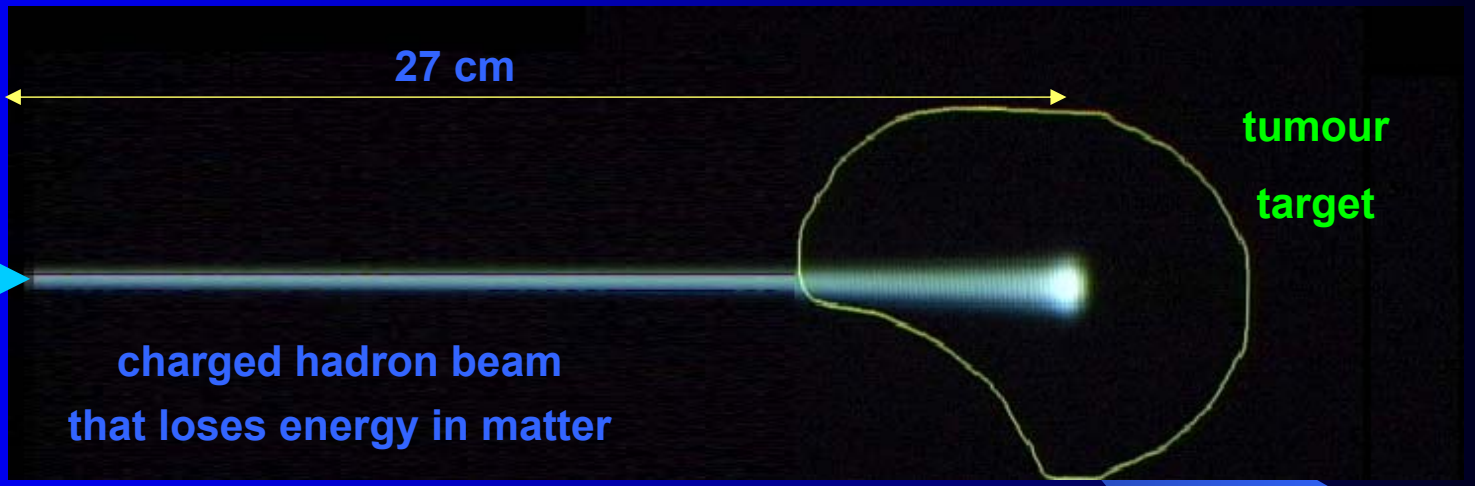
Hadrontherapy accelerators the rationale

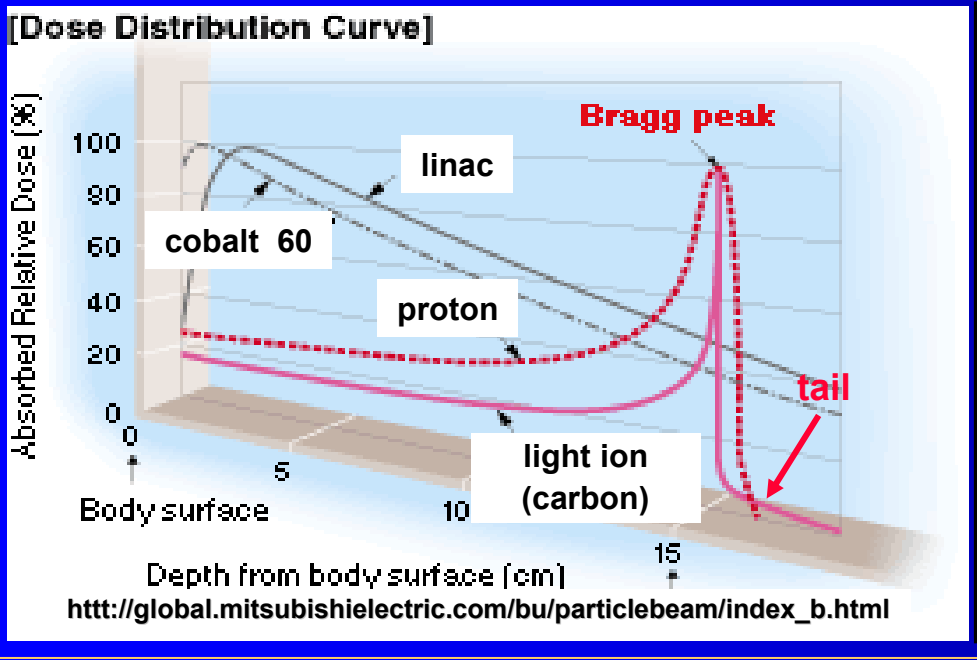
www.cern.ch/cerimed/

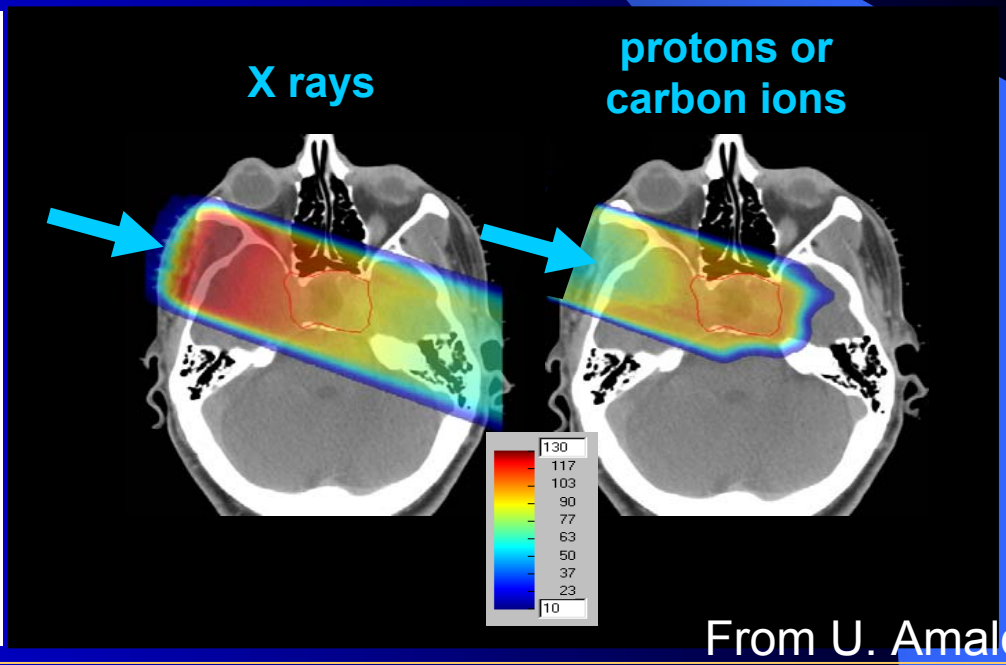
200 MeV - 1 nA protons

4800 MeV – 0.1 nA carbon ions

which can control radioresistant tumours







From U. Amaldi

European Network for LIGht Ion Therapy; 2002-2005

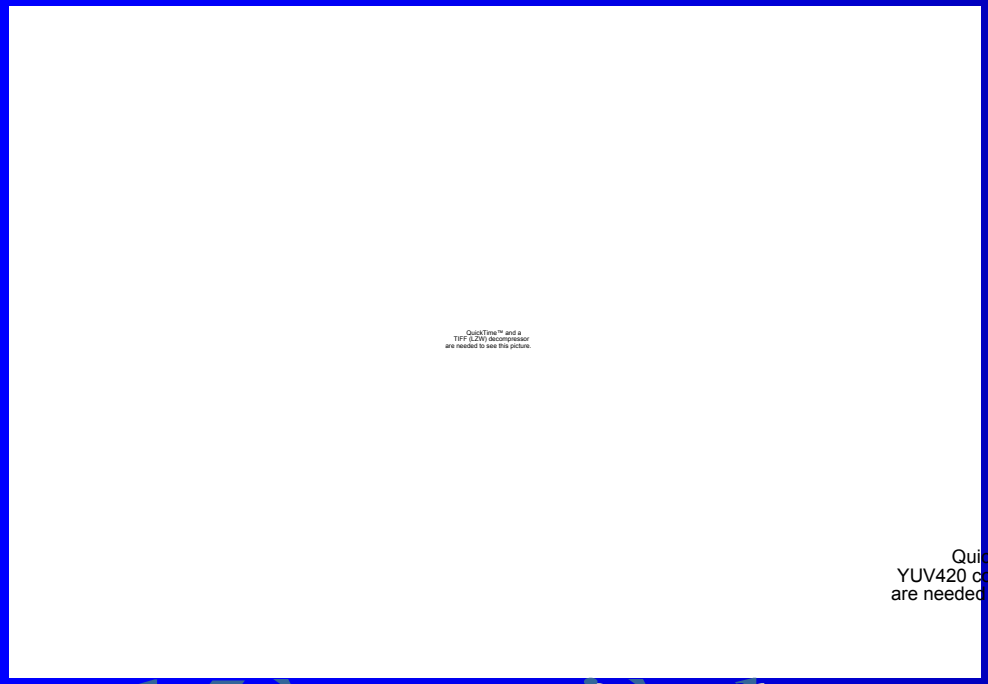
www.cern.ch/cerimed/

CERN, ESTRO, GSI and the five group of scientists promoting the projects in

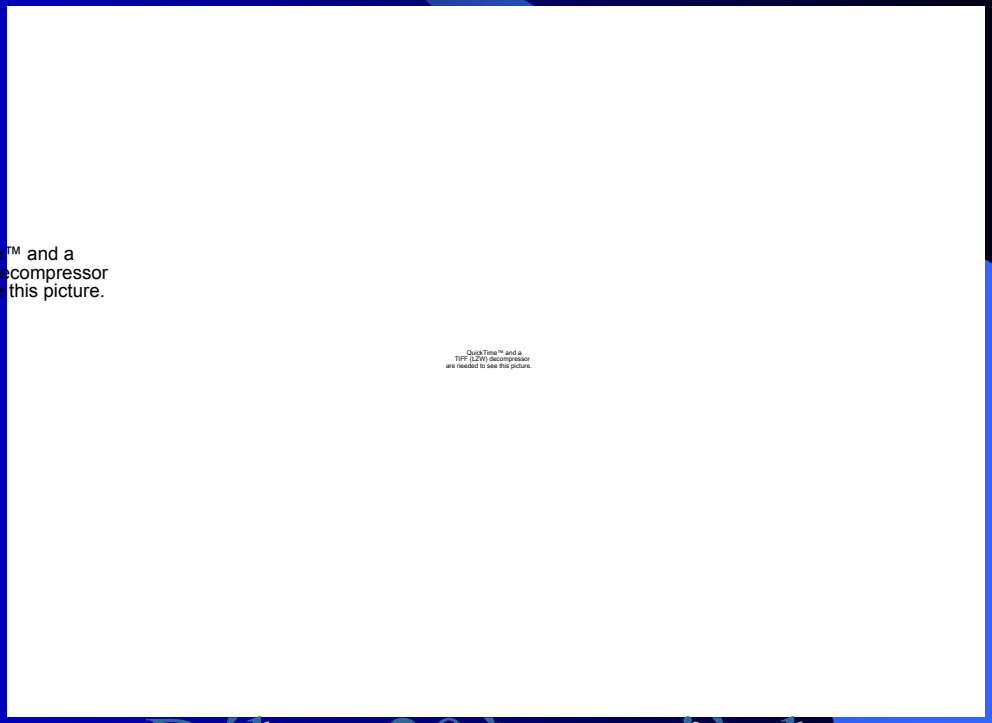
Heidelberg	**HIT**
Pave	**CNAO**
Wiener Neustadt	**MedAustron**
Lyon	**ETOILE**
Stockholm	

have woked together on clinics, radiobiology, physics and engineering items

In-vivo imaging from past to present and future



15ème siècle

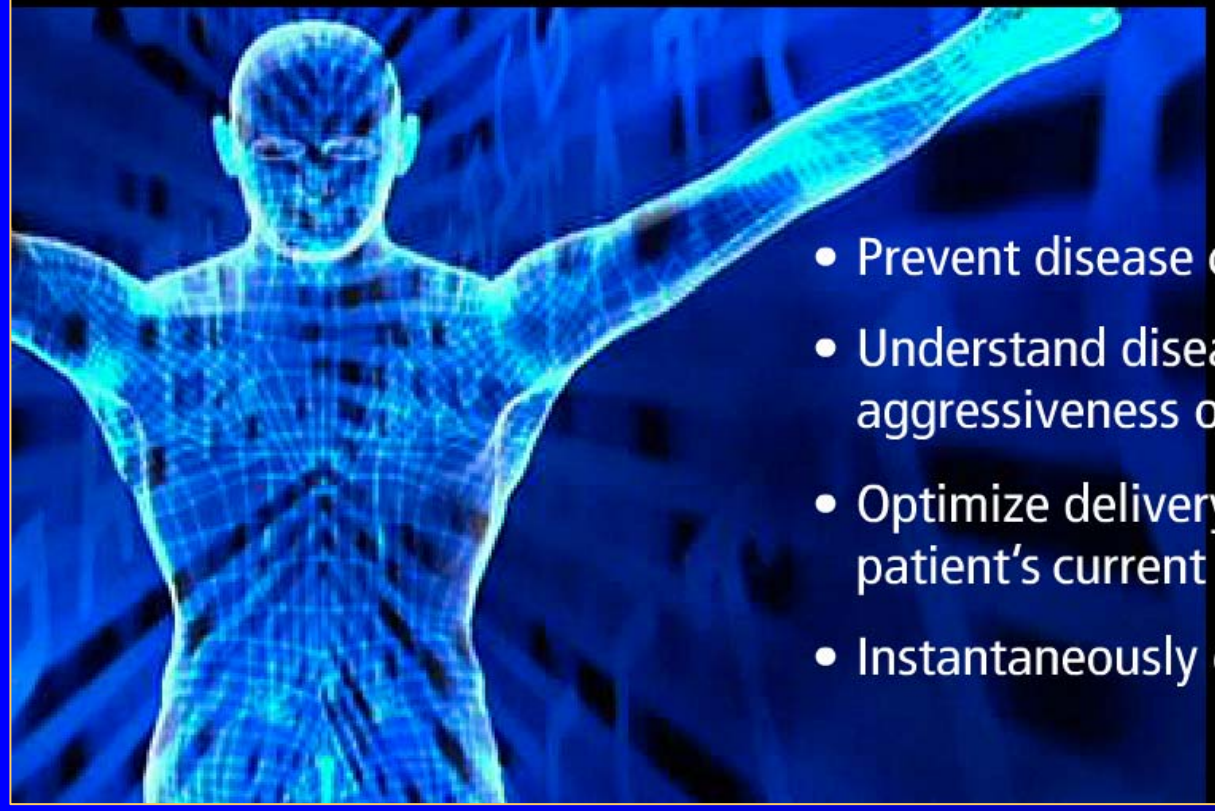


Début 20ème siècle

The future Healthcare Mission

www.cern.ch/cerimed/

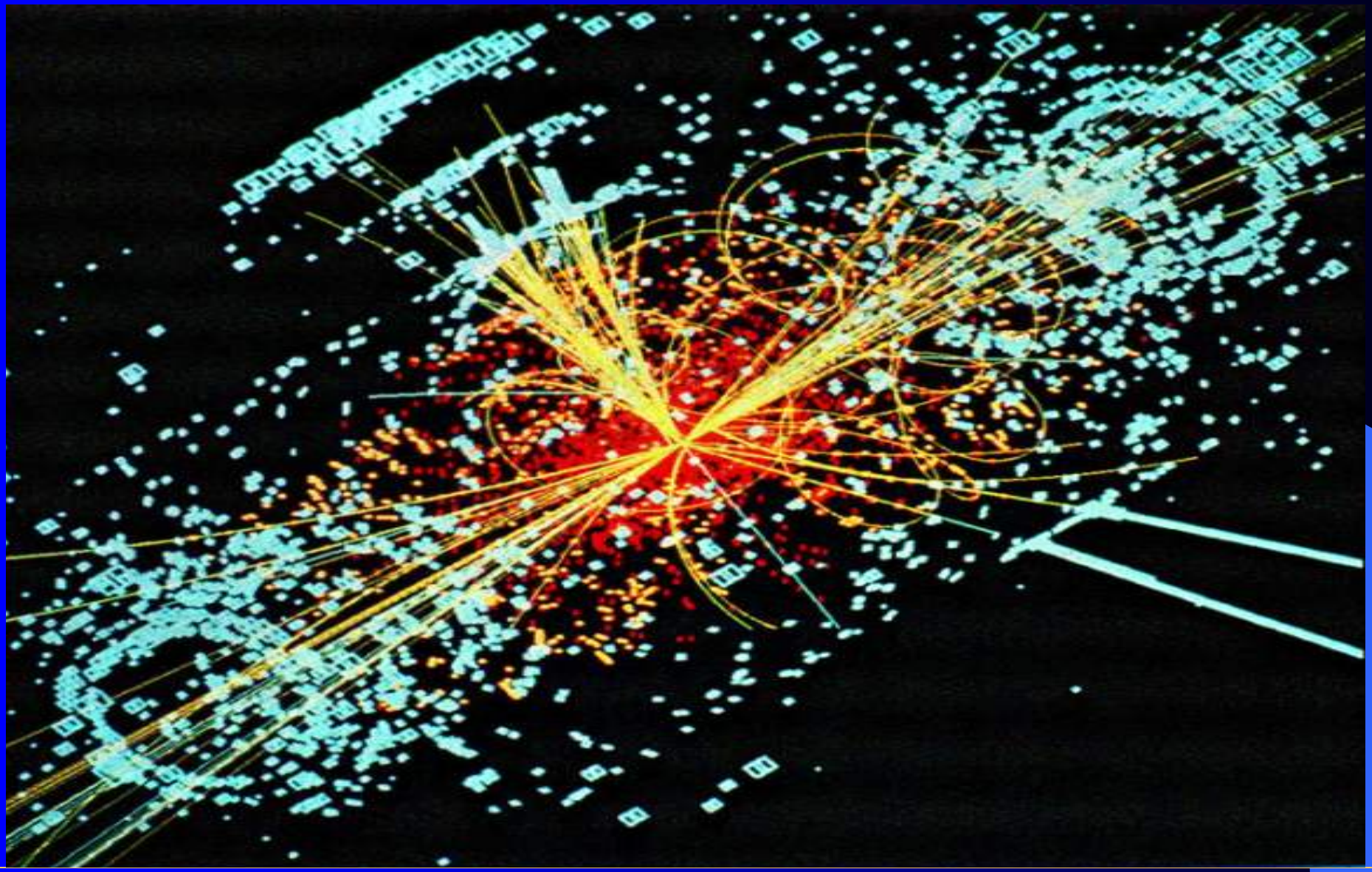
We need to capture enough information from each individual person to:



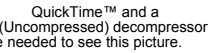
- Prevent disease or diagnose it at its earliest stage
- Understand disease parameters, such as aggressiveness or metastatic potential
- Optimize delivery of therapy based on the patient's current biologic system
- Instantaneously evaluate therapeutic effectiveness

Requires a "new generation" of imaging devices and bioengineering…

Simulation of a Higgs in CMS



CMS Installation

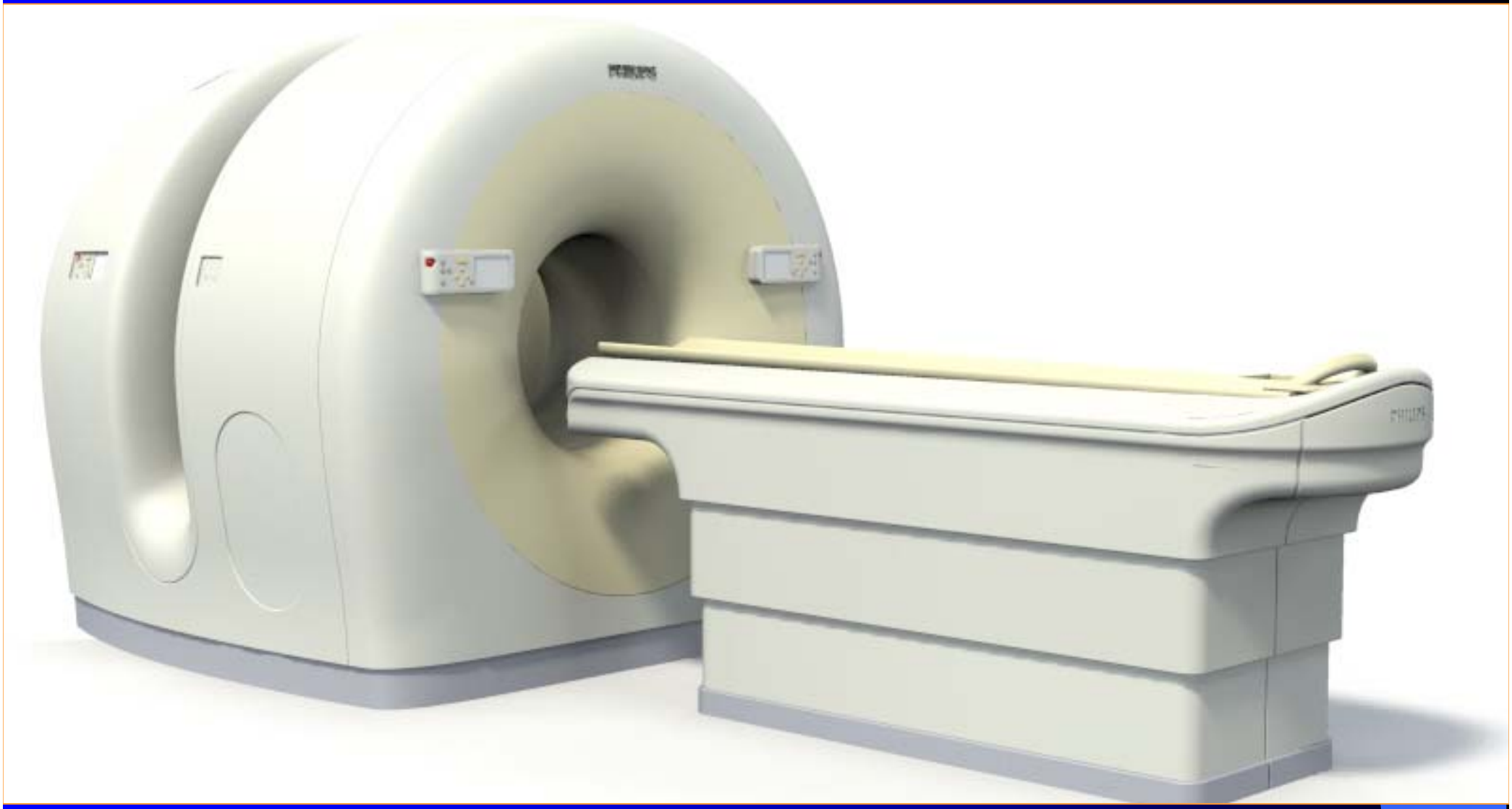


Non invasive anatomic + functional imaging

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Patient treated for a colon cancer and revealing under PET/CT scan an additional breast cancer

Modern PET/CT

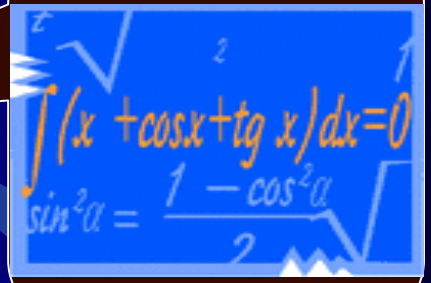


Medical Imaging: a multidisciplinary approach

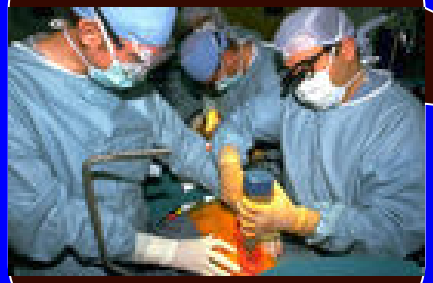
www.cern.ch/cerimed/

Physics

Mathematics

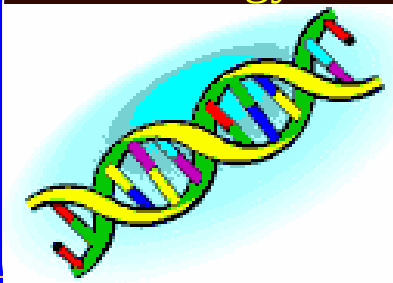


Medicine



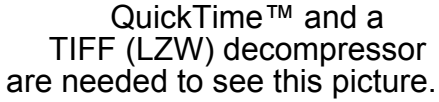
Chemistry

Biology



Informatics

Combine anatomic and fonctional informations



Université de Genève

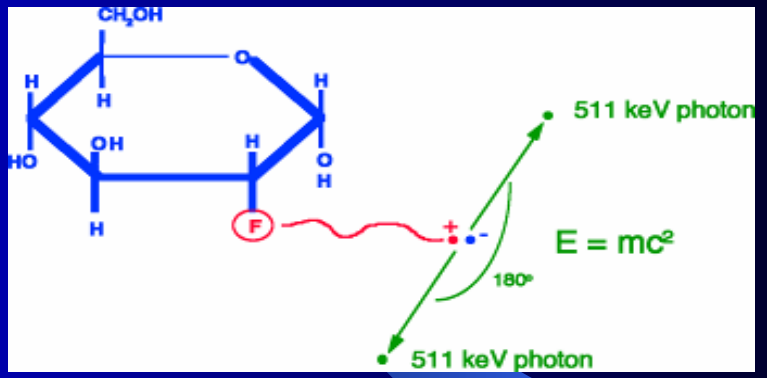
PET Molecular Imaging

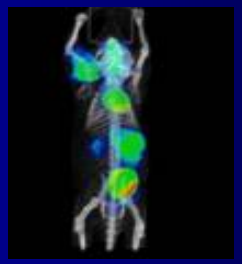
www.cern.ch/cerimed/

Accelerator

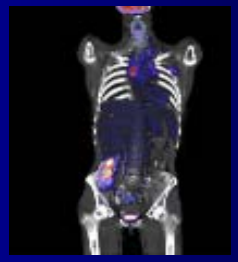
^{15}O
^{13}N
^{11}C
^{18}F

2-[F-18]Fluoro-2-Deoxy-D-Glucose (FDG)





Pre-Clinical



Clinical

From HEP detectors to Medical Imaging

www.cern.ch/cerimed/

Requirements for HEP EM calorimetry

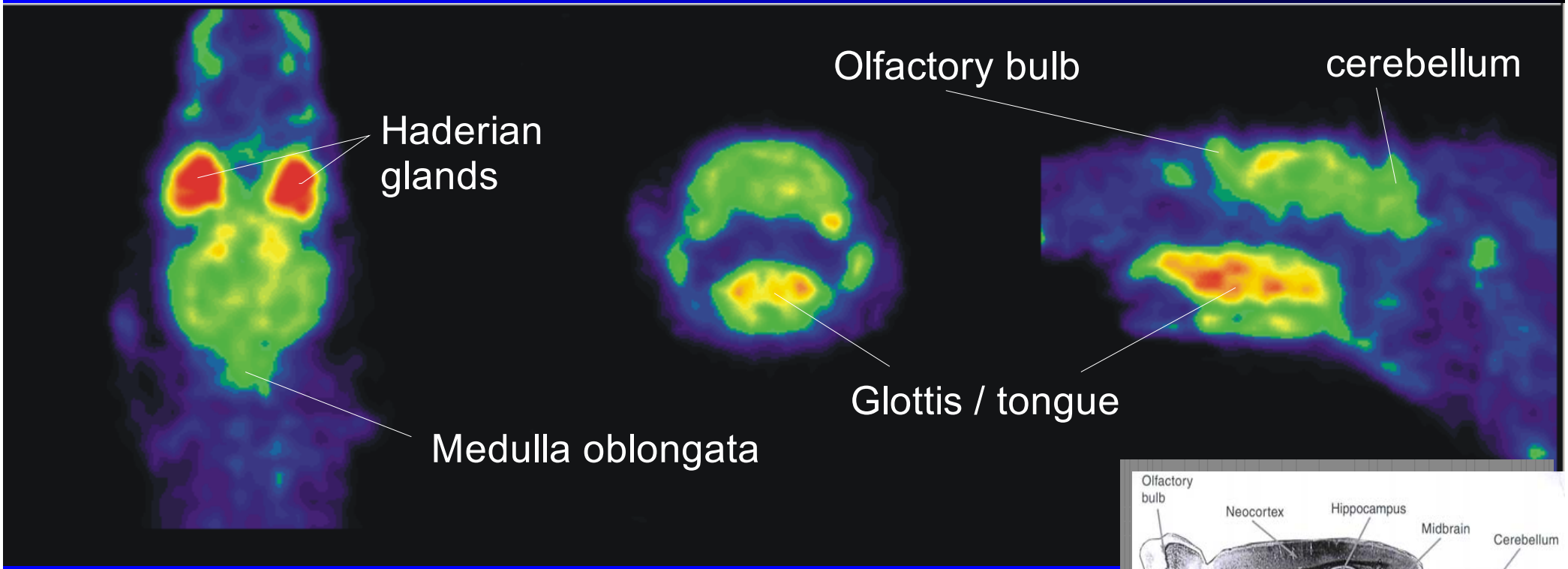
1. **Crystals** — Technology transfer
   - High density (> 6 g/cm^3)
   - Fast emission (< 100 ns), visible spectrum
   - Moderate to high light yield
   - High radiation resistance
2. **Photodetectors** — Technology transfer
   - Compact
   - High quantum efficiency and high gain
   - High stability
3. **Readout electronics** — Technology transfer
   - Fast shaping, low noise
   - Highly integrated
4. **Intelligent and parallel DAQ** — Technology transfer
   - Reduce dead time
5. **Software** — Technology transfer
   - Accurate Monte Carlo simulation
6. **General design** — Technology transfer
   - Compact integration of a large number of channels (> 10'000)

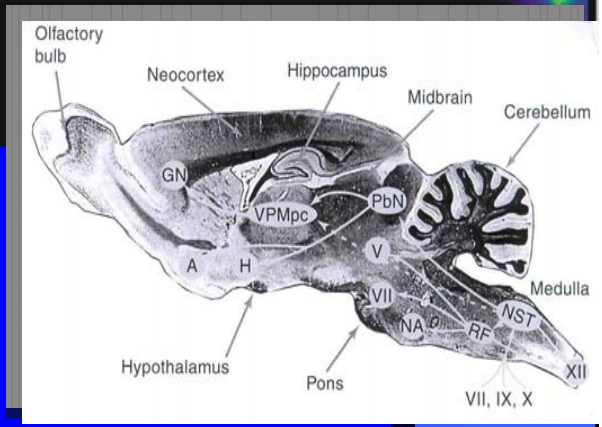
Requirements for Medical Imaging

1. **Crystals**
   - High density (> 7 g/cm^3)
   - Fast emission (< 100 ns), visible spectrum
   - High light yield
   - Moderate radiation resistance
2. **Photodetectors**
   - Compact
   - High quantum efficiency and high gain
   - High stability
3. **Readout electronics**
   - Fast shaping, low noise
   - Highly integrated
4. **Intelligent and parallel DAQ**
   - Reduce dead time
5. **Software**
   - Accurate Monte Carlo simulation
6. **General design**
   - Compact integration of a large number of channels (> 10'000)

ClearPET®, small animal PET Crystal Clear Collaboration

www.cern.ch/cerimed/





Rat brain FDG image

Towards Molecular Imaging

ANATOMICAL IMAGING → **FUNCTIONAL IMAGING** → **MOLECULAR IMAGING**

Visual representation, characterization and quantification of biological processes at the cellular and sub cellular level within living organisms.

- Gene expression (genomics, proteomics, transcriptomics, enzymatic activity, etc…)
- Molecular signal transduction through cell membranes

- Target specific cell receptors that are over-expressed in pathological situations (ex. neo-angiogenesis
- Multiple imaging capture techniques (Nuclear medicine/PET, MRI, MRS, Optical,…)

MACROSCOPIC MICROSCOPIC

Molecular Imaging in Medicine & Biology

www.cern.ch/cerimed/

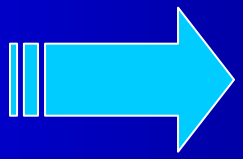
- Molecular Imaging to answer challenge of modern biology
  - –Access real time genomics through ***in vivo*** imaging of molecular process
  - –Detect early transformations in a cell, which may lead to pathology (precancerous activity)
  - –Early detection, prognosis, treatment selection, response to therapy
  - –Identify molecular pathways from gene to disease (genomics, proteomics)
    - »Novel molecular targets
    - »Specific genetic pathways
    - »Signal transduction
    - »Cell cycle alteration
    - »Angiogenesis
    - »Apoptosis

Requires specific effort on imaging instrumentation Sensitivity, Spatial and Temporal resolution

Requires targeting the cellular activity with specific contrast agents

The future of medical imaging

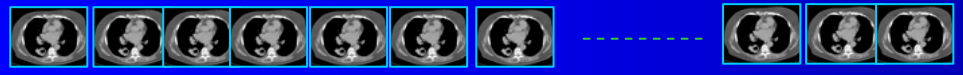
- Faster exams
- Movement correction
  - Breathing
  - Cardiac beating
  - Digestive bolus
- Dynamics
- Quantification
- True multimodality
- Reduce dose to patient



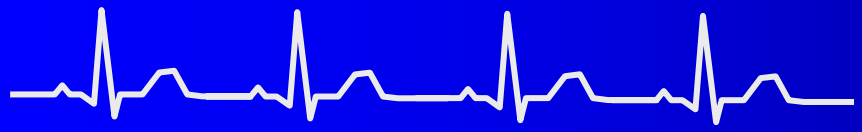
IMPROVE

- Spatial resolution
- Timing resolution
- Sensitivity
- Signal/Noise ratio

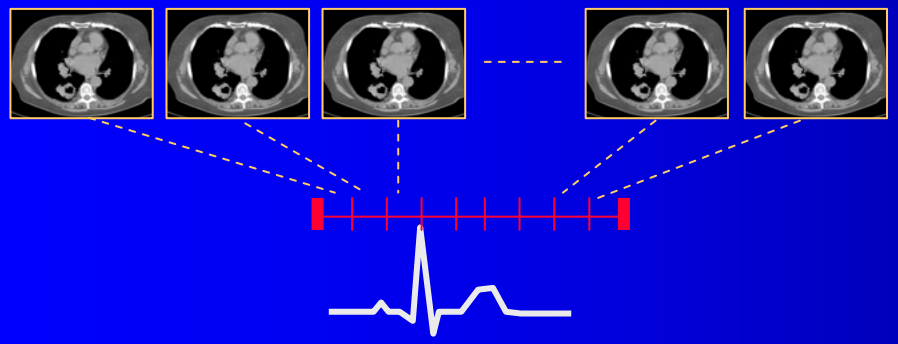
Cardiac CT



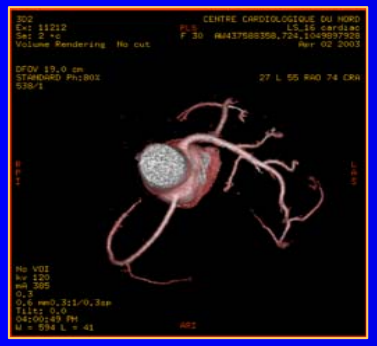
DYNAMIC CT ACQUISIION

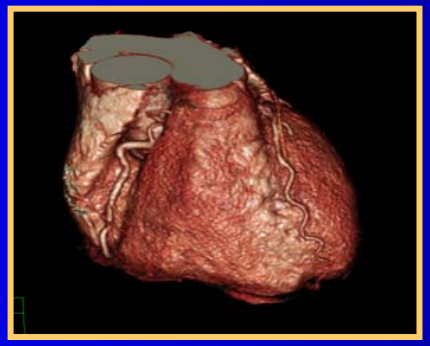


ECG



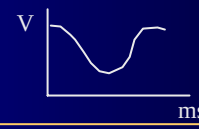
PHASES OF A CARDIAC CYCLE





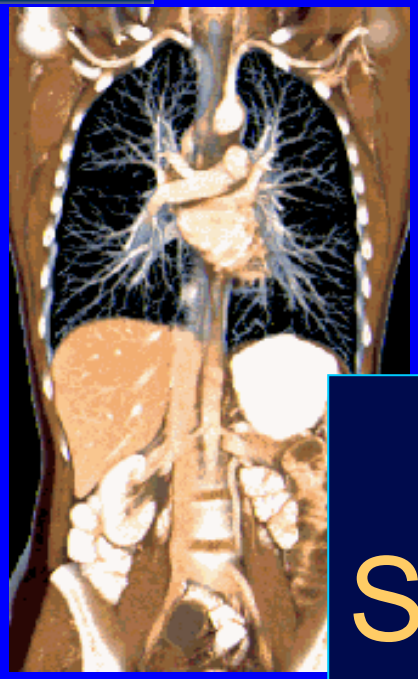
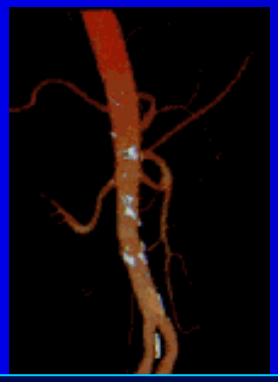
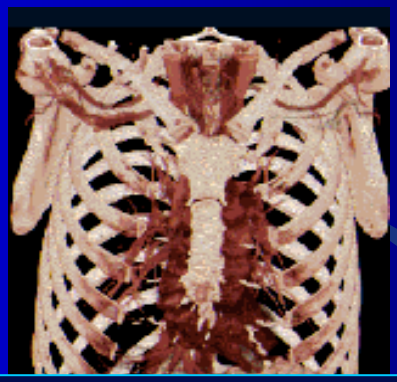
VOLUME RENDERED IMAGE OF HEART AND VESSELS

- EJECTION FRACTION
- CARDIAC OUTPUT
- REGIONAL WALL MOTION
- ..



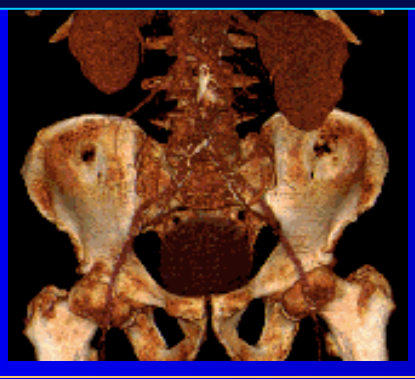
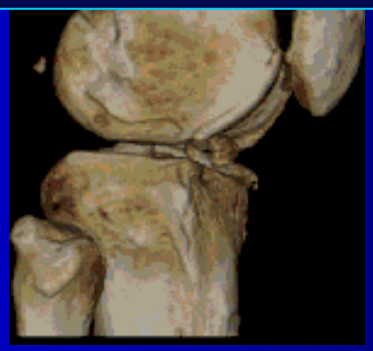
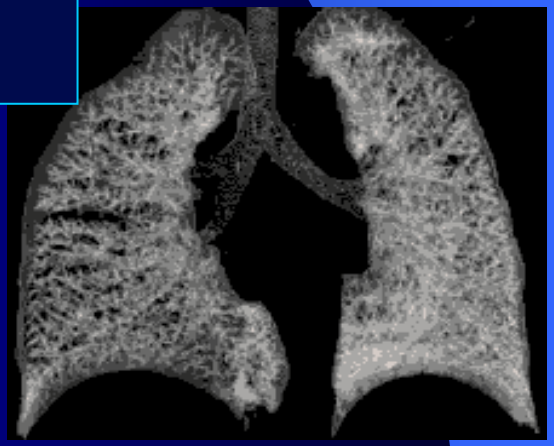
FUNCTIONAL PARAMETERS

Volumetric CT

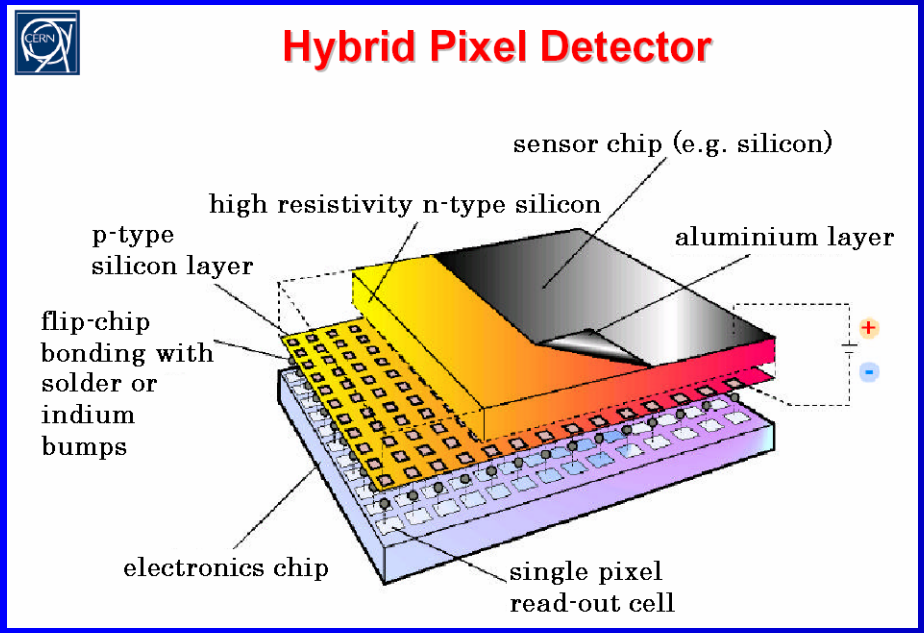
< 0,4 sec/ rotation
Organ in a sec (17 cm/sec)
Whole body < 10 sec

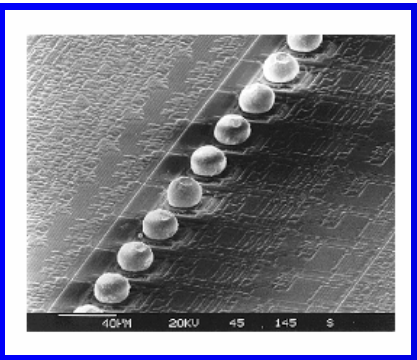
20 to 50 mSv
Standard radiography
0.1 mSv

Hybrid pixel detector Single photon counting

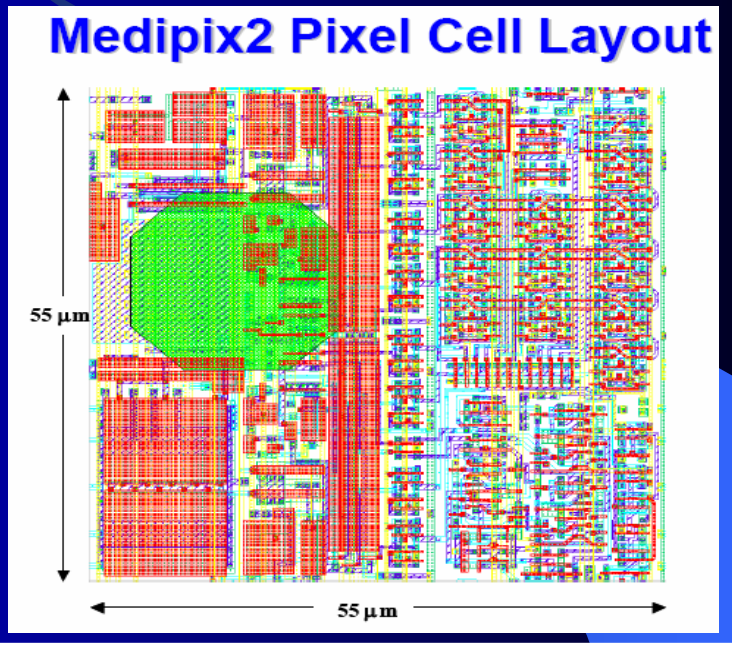
CMOS *technology*



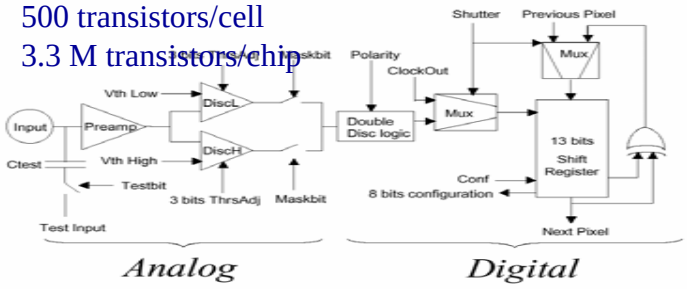


Bump-bonding: an industrial technology still posing yield problems

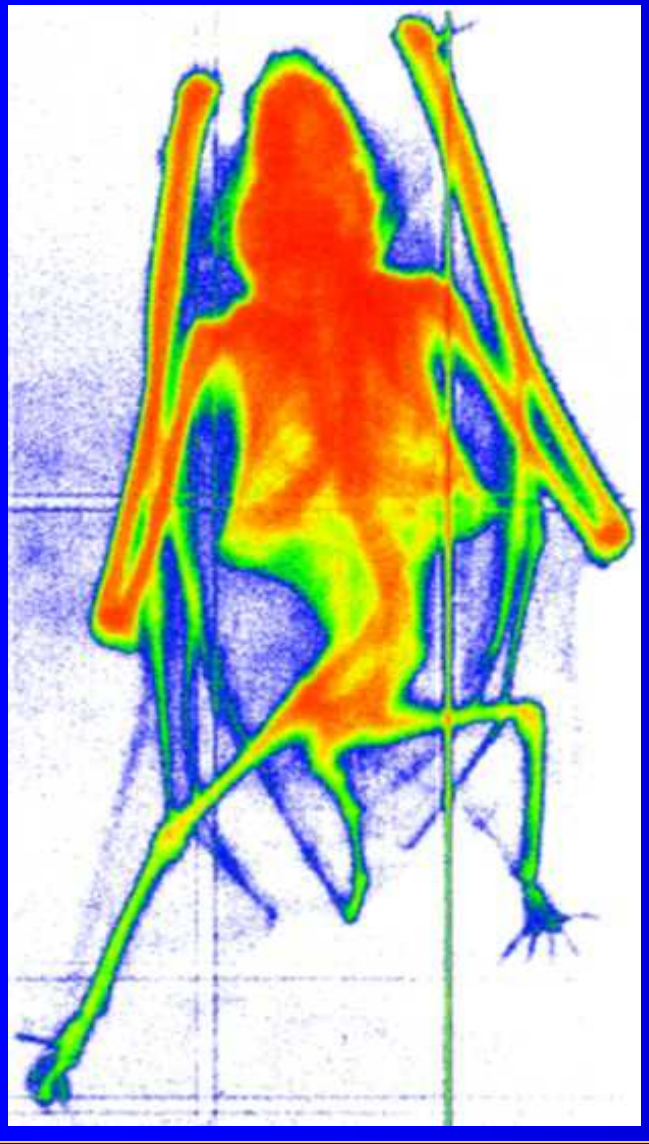
Medipix2 (55 µm pitch) 1 µm SACMOS
(M. Campbell et al.,1998)



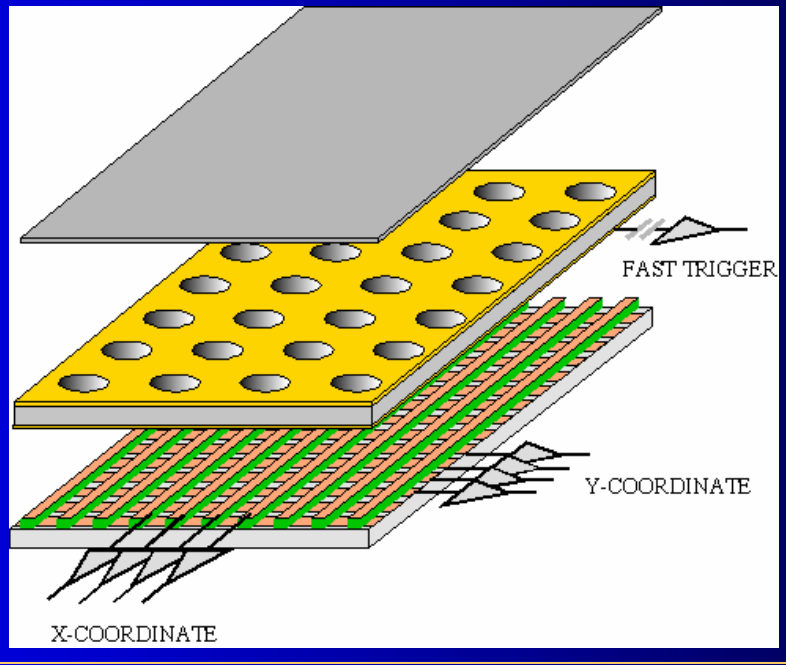
500 transistors/cell
3.3 M transistors/chip

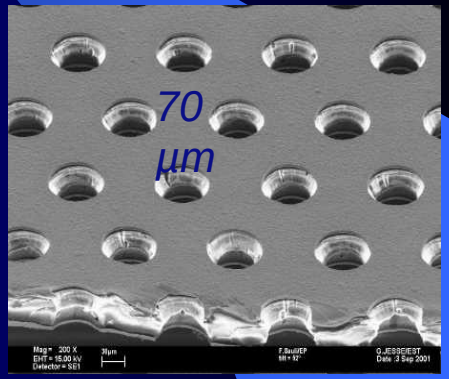


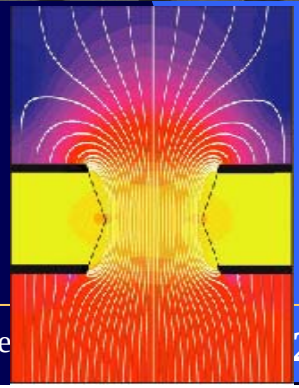
Also: GEM Detector



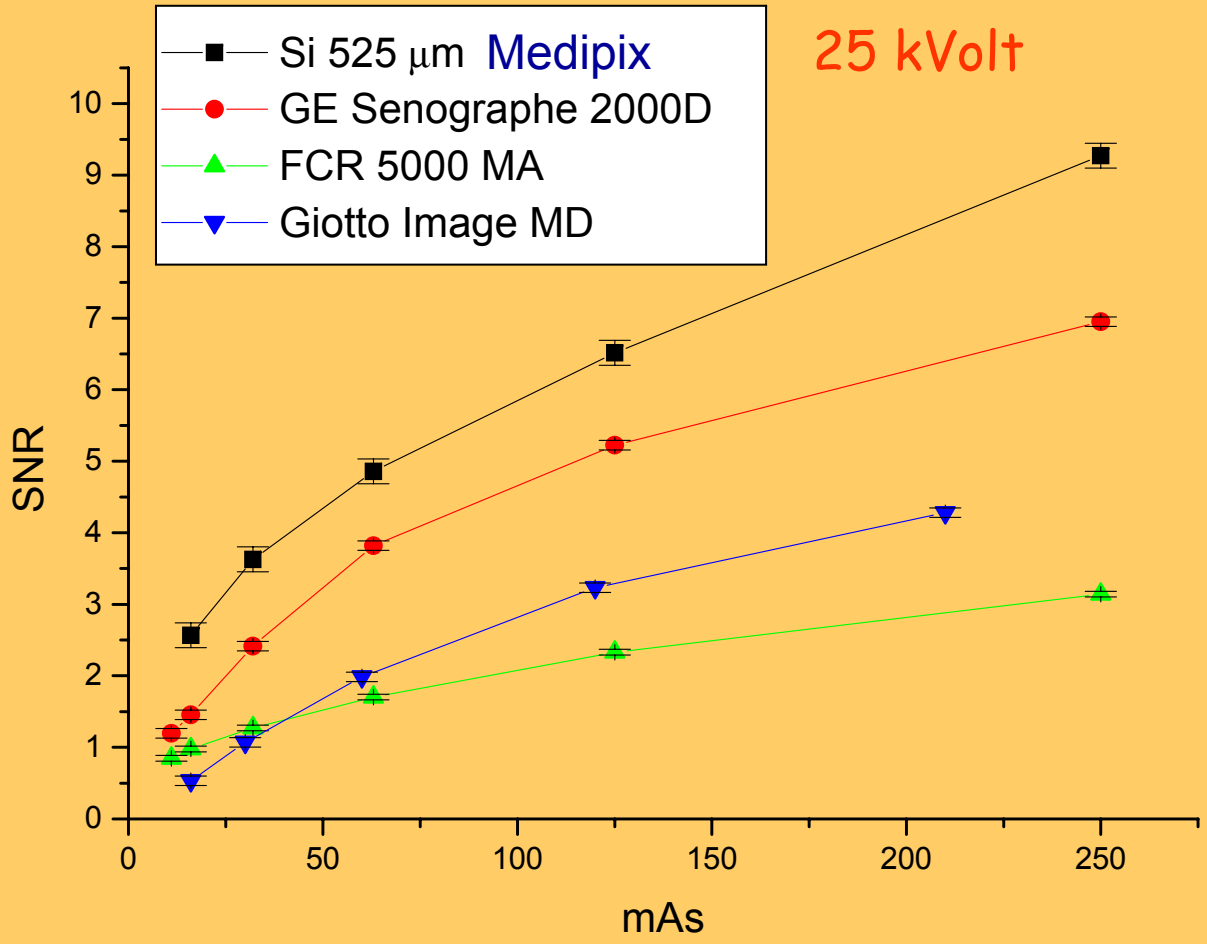
- Thin, metal-clad polymer foil, chemically pierced by a high density of holes (70-80 μm diameter).
- On application of a difference of potential between the two electrodes, electrons released by radiation in the gas on one side of the structure drift into the holes, multiply and transfer to a collection region.
- Cascading several foils results in high multiplication factors.







Single photon counting versus integrating digital radiography



- SNR for 2 mm thick tumor mass (RMI 156 phantom)

M. G. Bisogni et al., NIMA 546, 14 (2005)

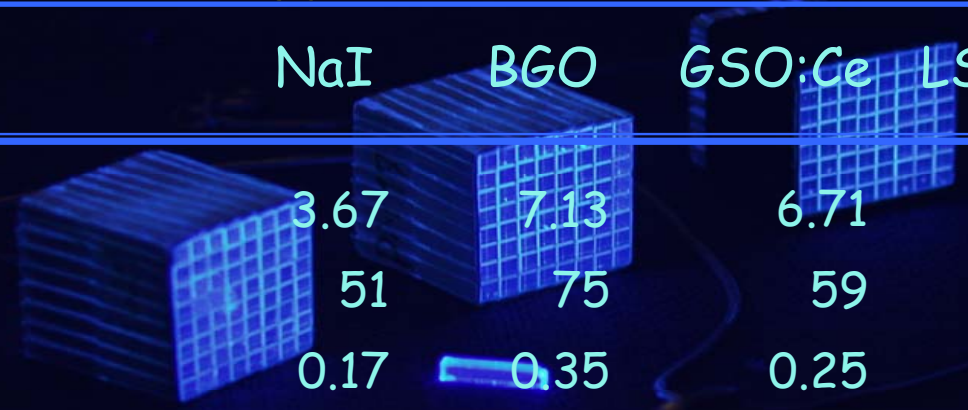
Statistical Noise in PET

- *25 psec* time stamp for accurate data sampling

- contributors to ToF Timing Resolution of 650 psec:
  - Crystal 450 psec
  - PMTs 100 psec
  - Other 100 psec

- **electronics design plays a key role in preserving the timing resolution**

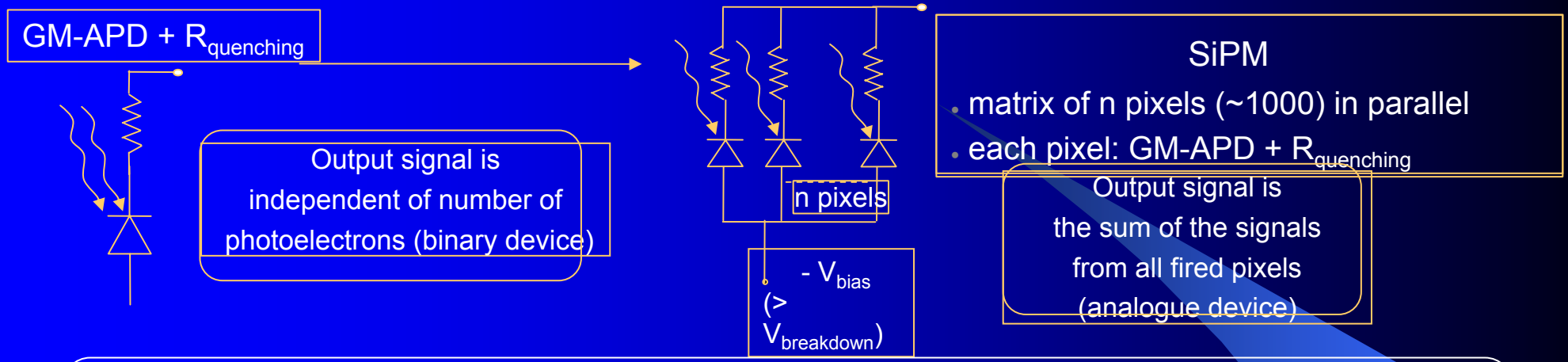
Scintillators for PET



Scintillators for PET

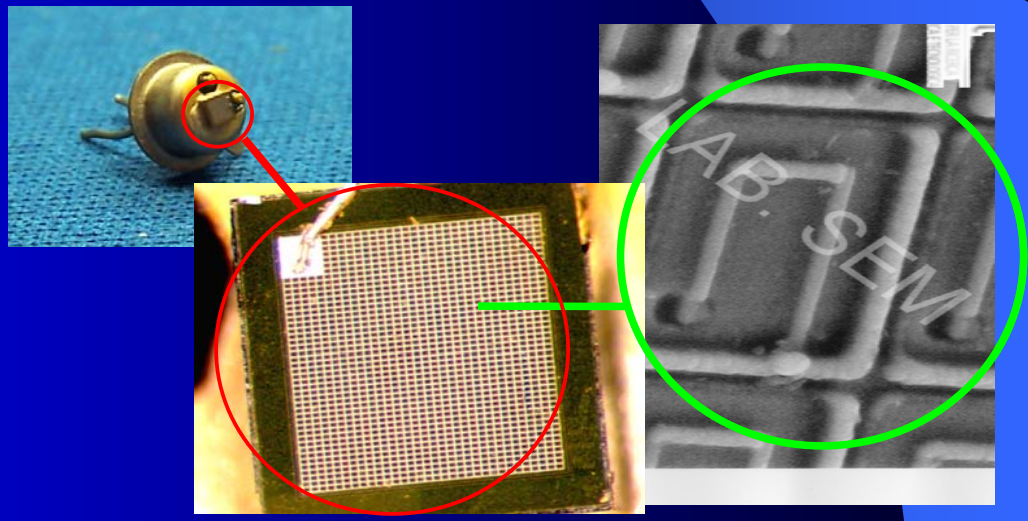
	1962	1977	1995	1999	2001
	NaI	BGO	GSO:Ce	LSO:Ce	LuAP:Ce
Density (g/cm^3)	3.67	7.13	6.71	7.40	8.34
Atomic number	51	75	59	66	65
Photofraction	0.17	0.35	0.25	0.32	0.30
Decay time (ns)	230	300	30-60	35-45	17
Light output (hν/MeV)	43000	8200	12500	27000	11400
Peak emission (nm)	415	480	430	420	365
Refraction index	1.85	2.15	1.85	1.82	1.97

Geiger mode APD (SiPM)



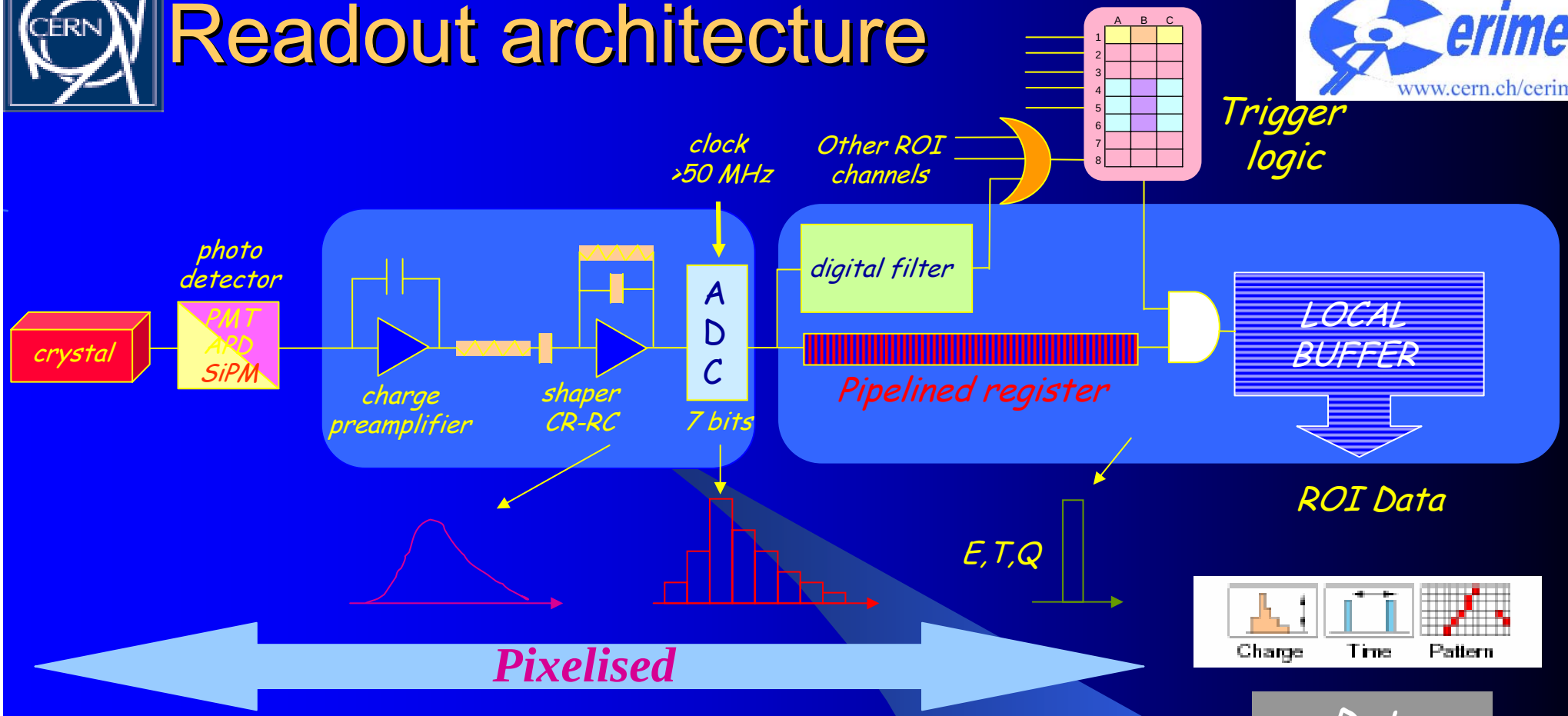
Result: high gain, low noise detector and proportional for $N_{photon} < N_{cells}$

- Excellent photon counting capability
- Fast response time (<1ns); small recovery time (~few ns)
- Noise (dark counts) limited to few photoelectron level
- Insensitivity to magnetic fields
- Compact and rugged



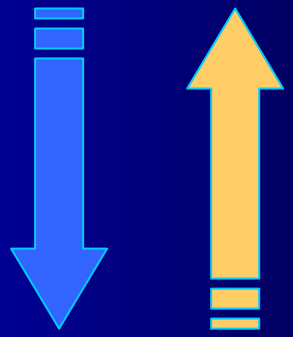
→ *Potential replacement for traditional vacuum-based PMT*

Readout architecture



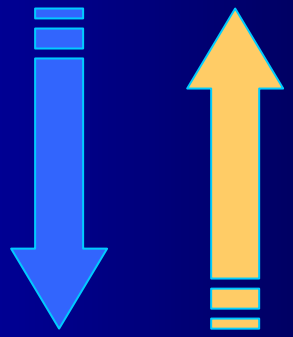
- Trigger logic processes "raw fast information"
- Free-running sampling ADC
- Digital filter used to extract pulse amplitude and high resolution timing
- Pipelined processing architecture to avoid deadtimes
- Only one "channel" to compute either the energy and time

Spin-off from particle detectors in the field of medicine and biology



Paul Lecoq
CERN, Geneva

Cross-fertilisation in the fields of particle detectors medicine and biology



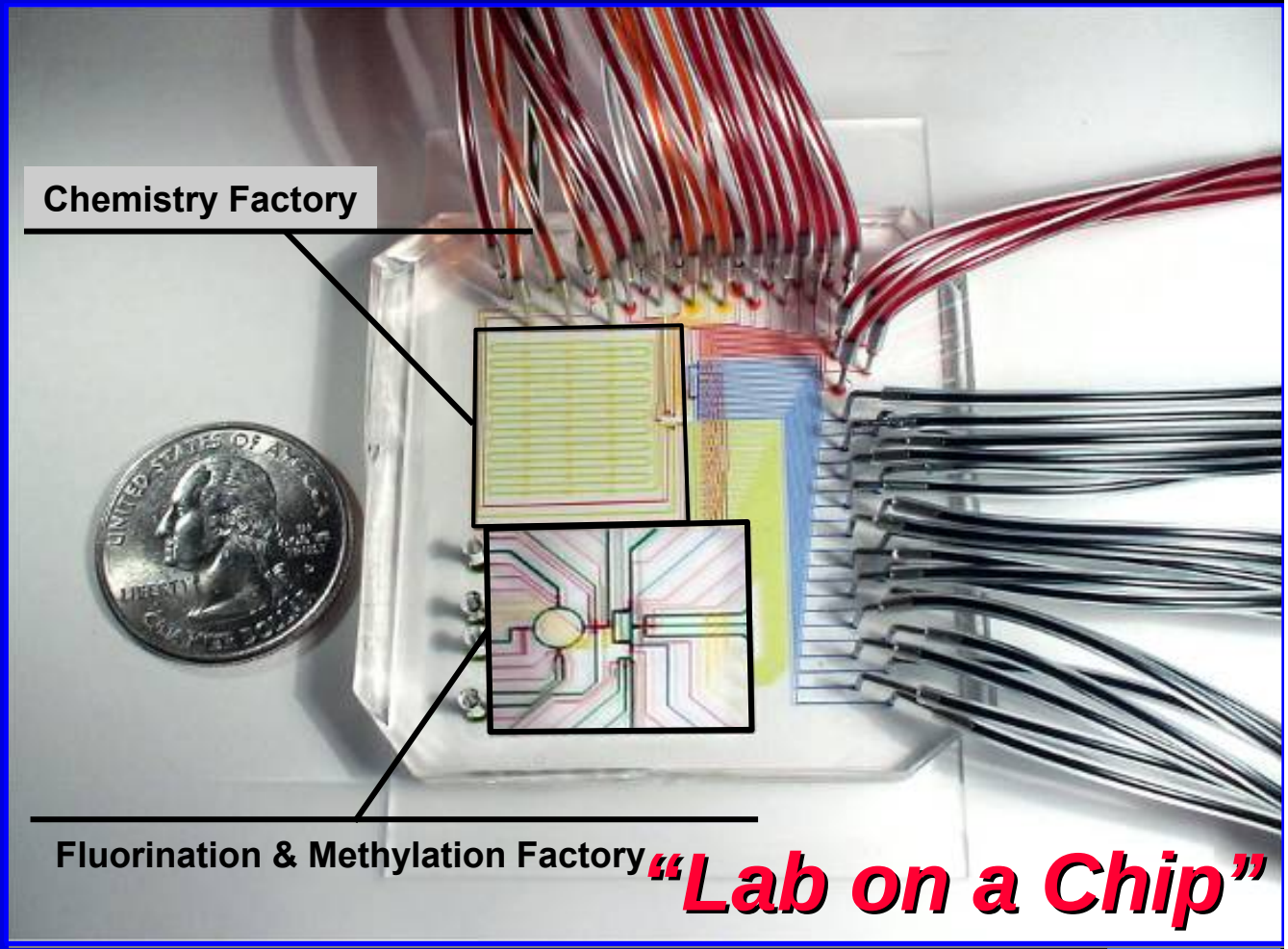
Paul Lecoq
CERN, Geneva

Cross-fertilisation in the fields of particle detectors medicine and biology

Paul Lecoq
CERN, Geneva

Automated Radio-chemistry

www.cern.ch/cerimed/

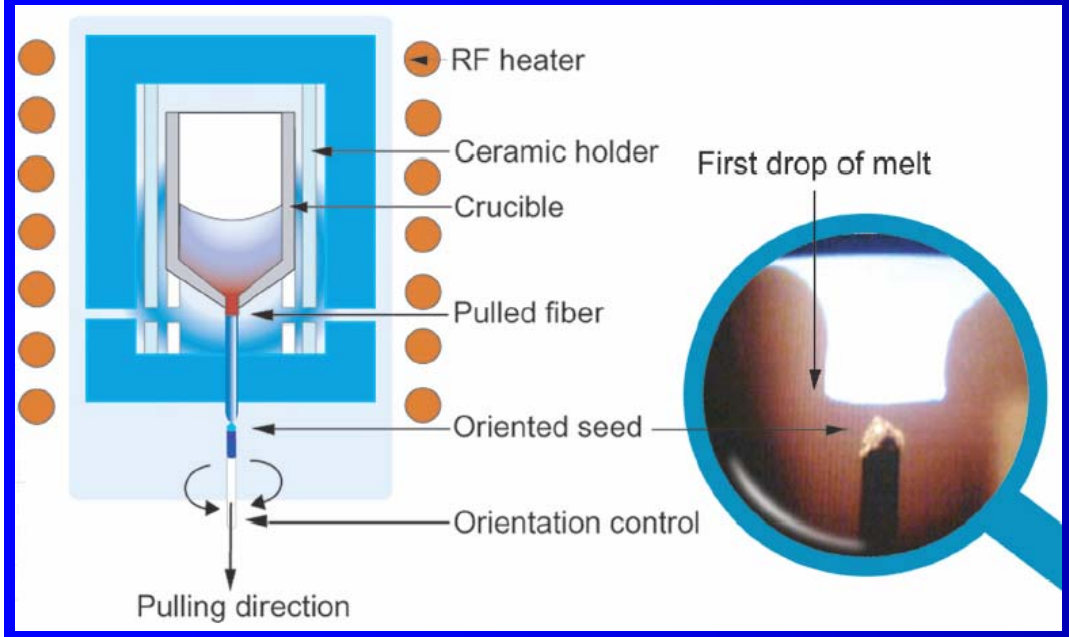


Next generation of high spatial resolution small animal PET

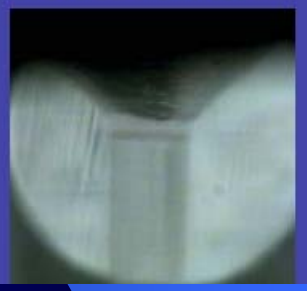
www.cern.ch/cerimed/

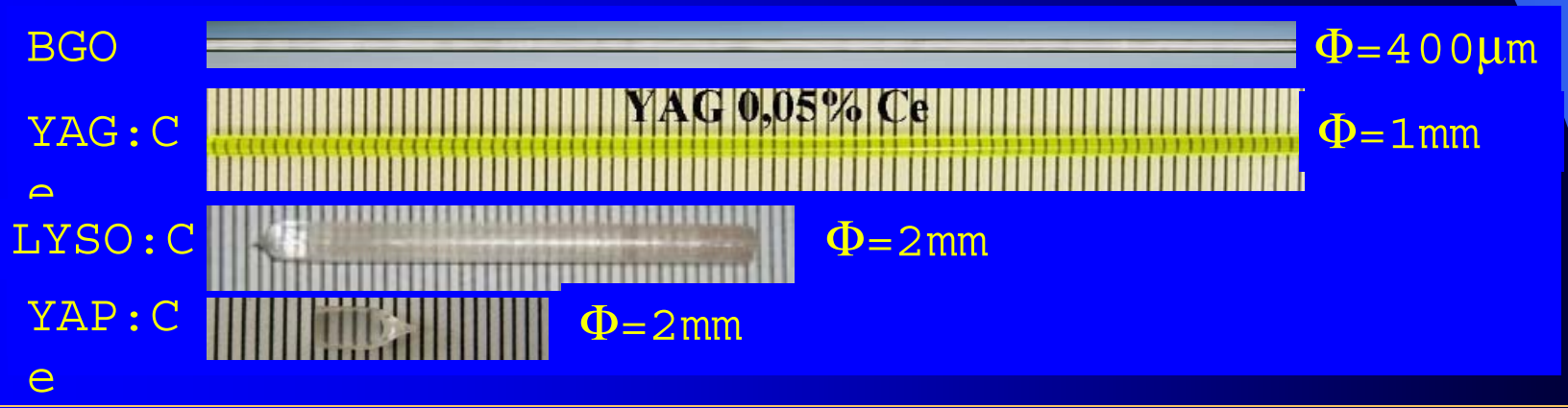
➔ **Towards smaller pixel cross section**

Micro-pulling-down crystal fiber growth



Crucible and fiber





The DREAM Calorimeter

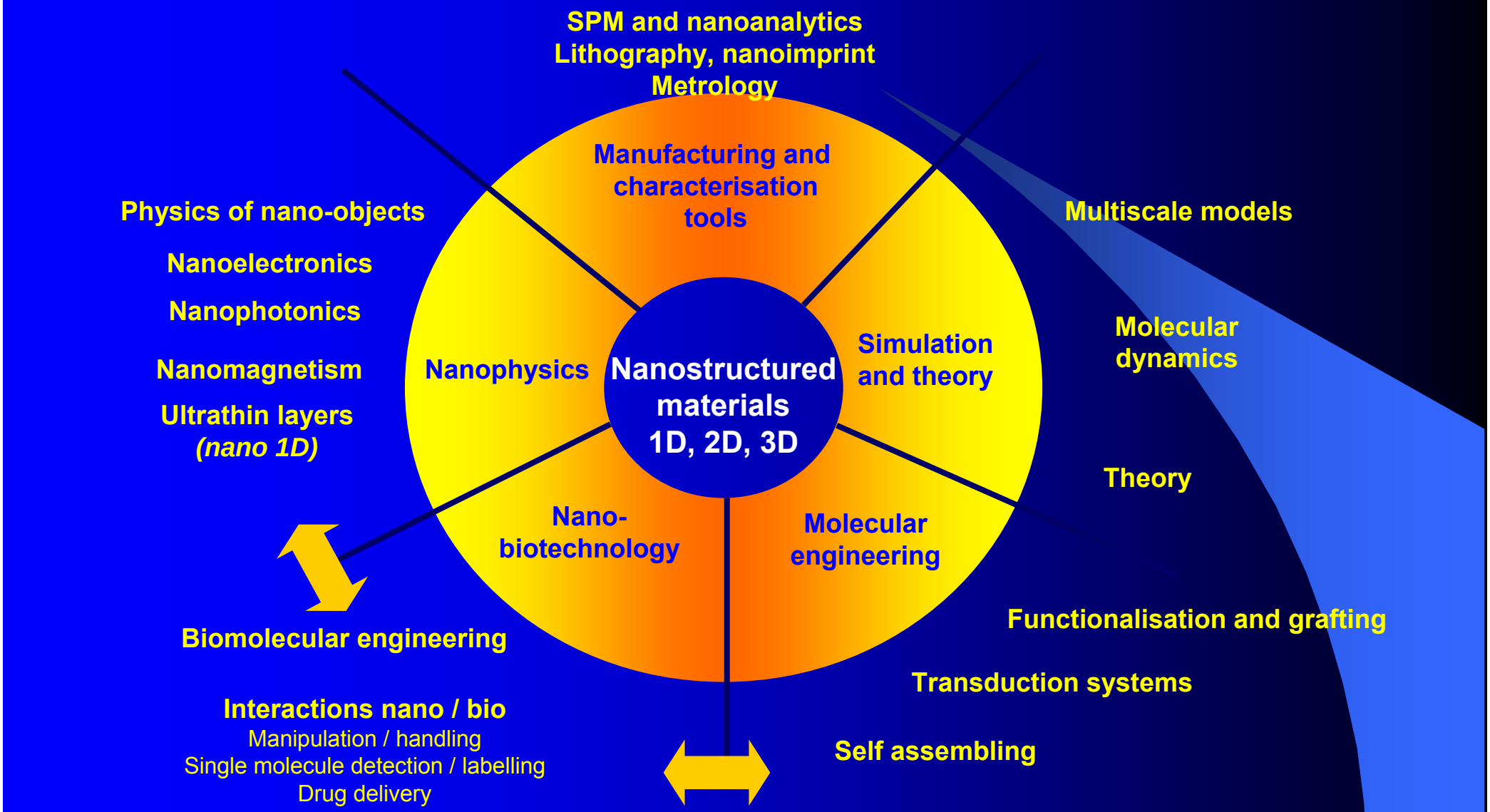
QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

From R. Wigmans

Towards a new concept of "analytical" calorimetry ?

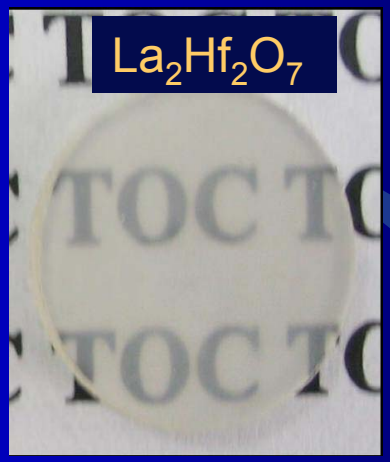
- Following the idea of the DREAM Calorimeter proposed by R. Wigmans
- Concept of an "homogeneous" calorimeter with precise information about electromagnetic/hadronic/neutron ratio
- Cables made of bundles of heavy scintillating fibres of different composition
  - LSO:Ce scintillating fibres: e + h
  - LSO undoped fibres: Cerenkov (e only) n=1.82 (1.45 for quartz)
  - LBO ($Li_2B_4O_6$:Ce) : neutrons

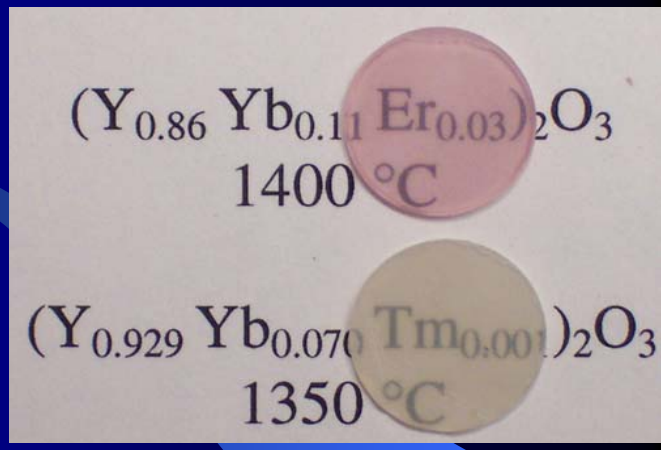
Nanotechnology
An interdisciplinary field



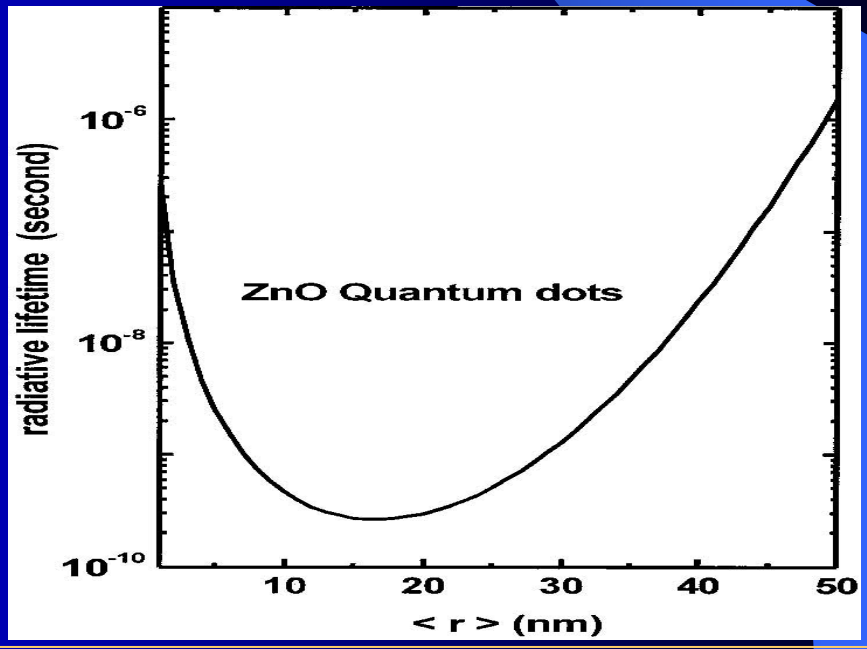
Nanotechnologies for a new generation of scintillators

- Prereacted nanopowders for low temperature production of high quality ceramic





- Ultrafast nanocrystals and quantum dots



Nanodevices used as contrast and/or therapeutic agents

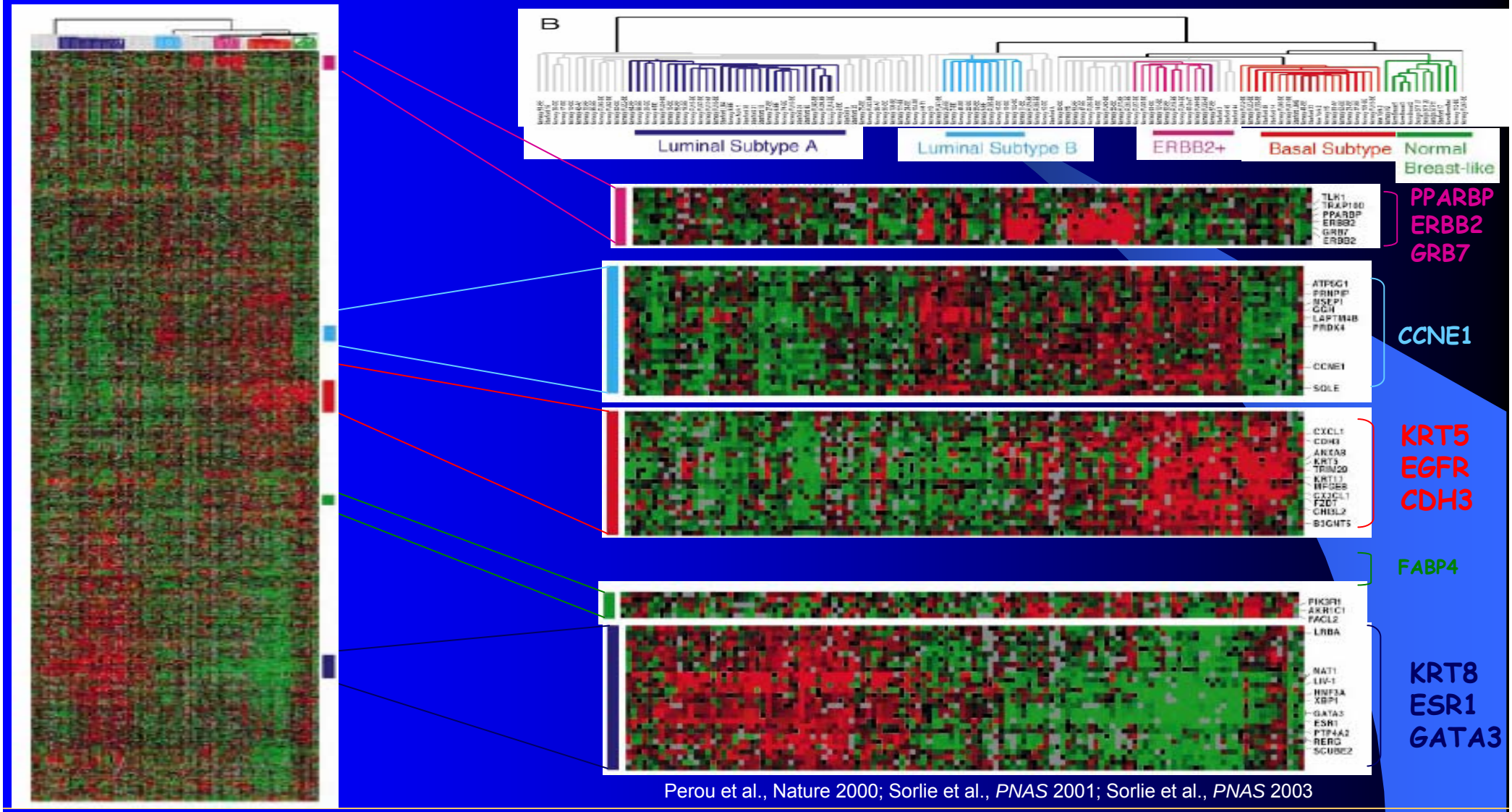
Quantum Dots
Tiny spheres of semiconducting materials
the diameter of which is smaller
than the Bohr radius of the exciton (nm range)

This gives them extraordinary optical properties
like λem directly proportional to the QDot radius

Quantum Dots
A possible way to develop
compact metamaterials
with encoding the light signal
as a function of its emission coordinates ?

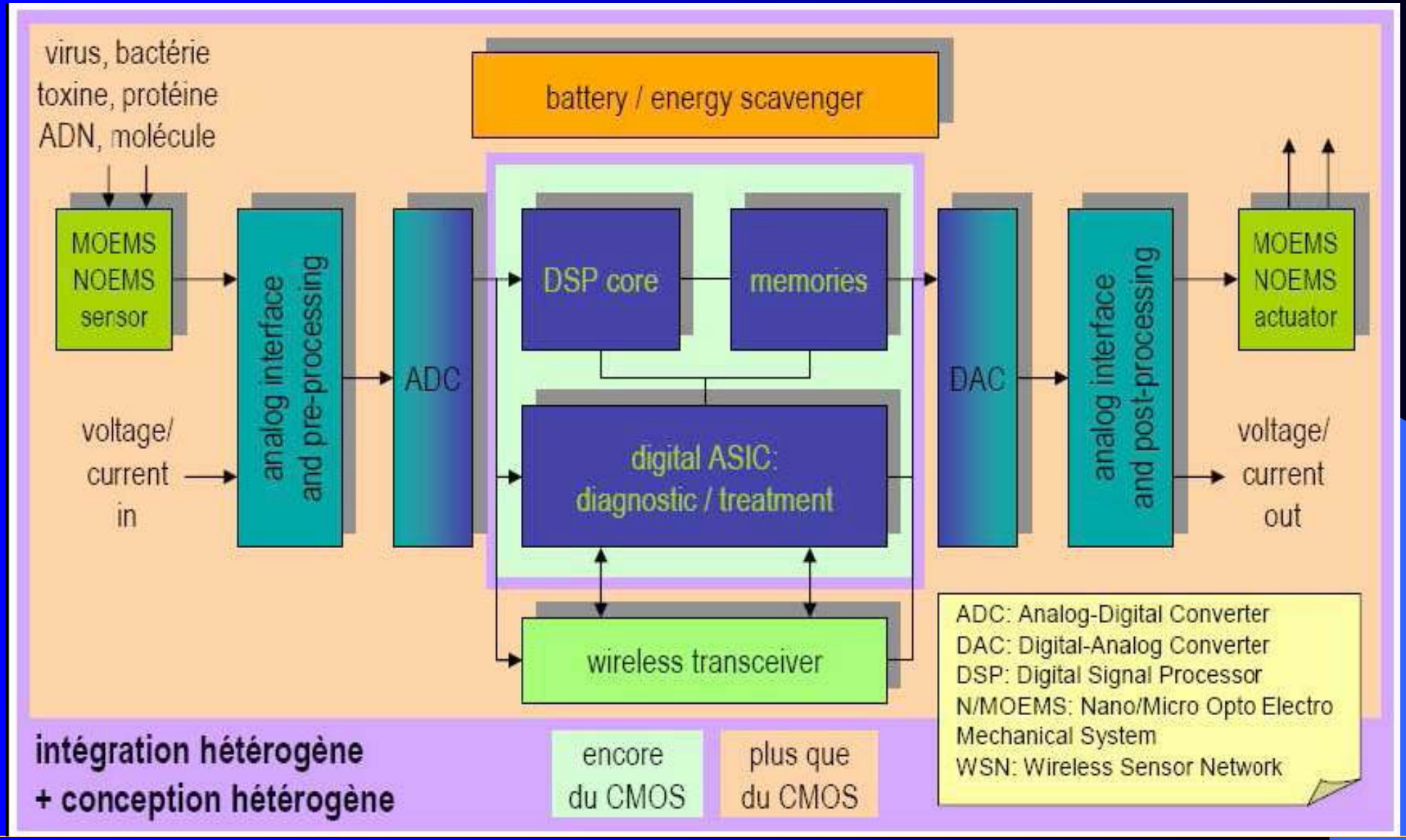
Micro-arrays and biochips

Molecular heterogeneity of Breast cancer



Perou et al., Nature 2000; Sorlie et al., *PNAS* 2001; Sorlie et al., *PNAS* 2003

Bioengineered materials



Conclusions

- HEP has a lot of knowledge and expertise to transfer in different areas with high societal impact like biology, medicine, homeland security, etc…

  ➢ This must be further encouraged

- HEP has a lot to learn from other scientific and industrial domains, which have very much progressed in the development of their own instrumentation using nanotechnologies, quantum optics, photonics, etc…

  ➢ This must be better organized

Tools and Science

"New directions in science are launched by new tools much more often than by new concepts.

The effect of a concept-driven revolution is to explain old things in new ways.

The effect of a tool-driven revolution is to discover new things that have to be explained."

Freeman Dyson, Imagined Worlds


Thank you

Can we do more?

- Technology transfer from HEP to medicine is strongly encouraged

BUT

- CERN and HEP community main mission is to do particle physics, not medical imaging
- A stronger coordination is needed and must be further developed between physicists, the biomedical world and industry
- A bridge must be built to integrate innovative technologies developed in HEP and other fundamental disciplines, and to validate them in complex systems in a biomedical environment
- No structure exists at the European level for this mission

Cerimed (European Centre for Research in Medical Imaging) could be a solution

European Centre for Research in Medical Imaging

www.cern.ch/cerimed/

Cerimed is NOT

- ***Just another lab promoting technology transfer activities in the field of medical imaging***

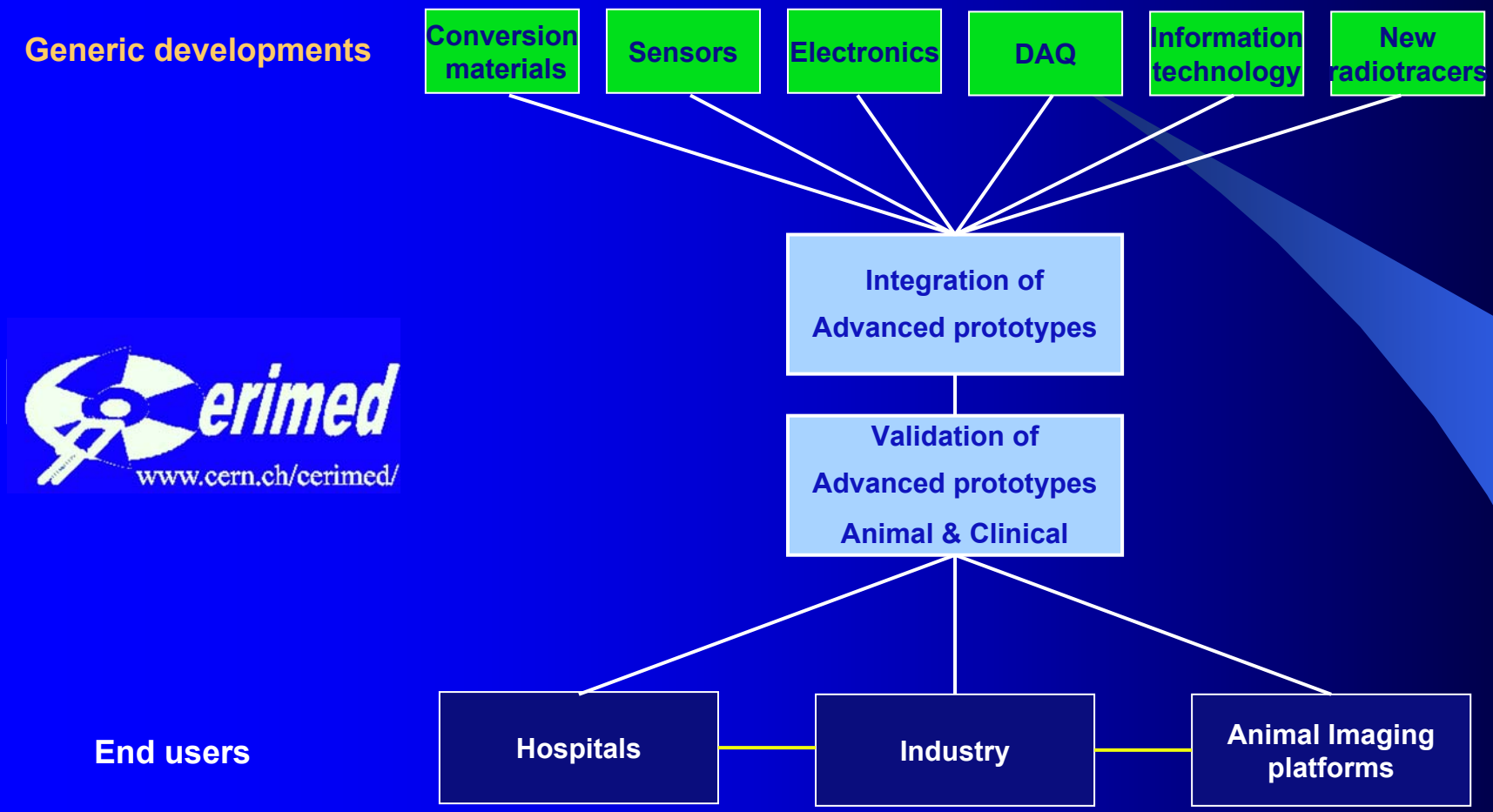
Cerimed is

- ***A place where european experimental programs and related R&D, agreed by the european medical imaging community and political authorities, are implemented in a coherent way through laboratory collaborations***

Objectives

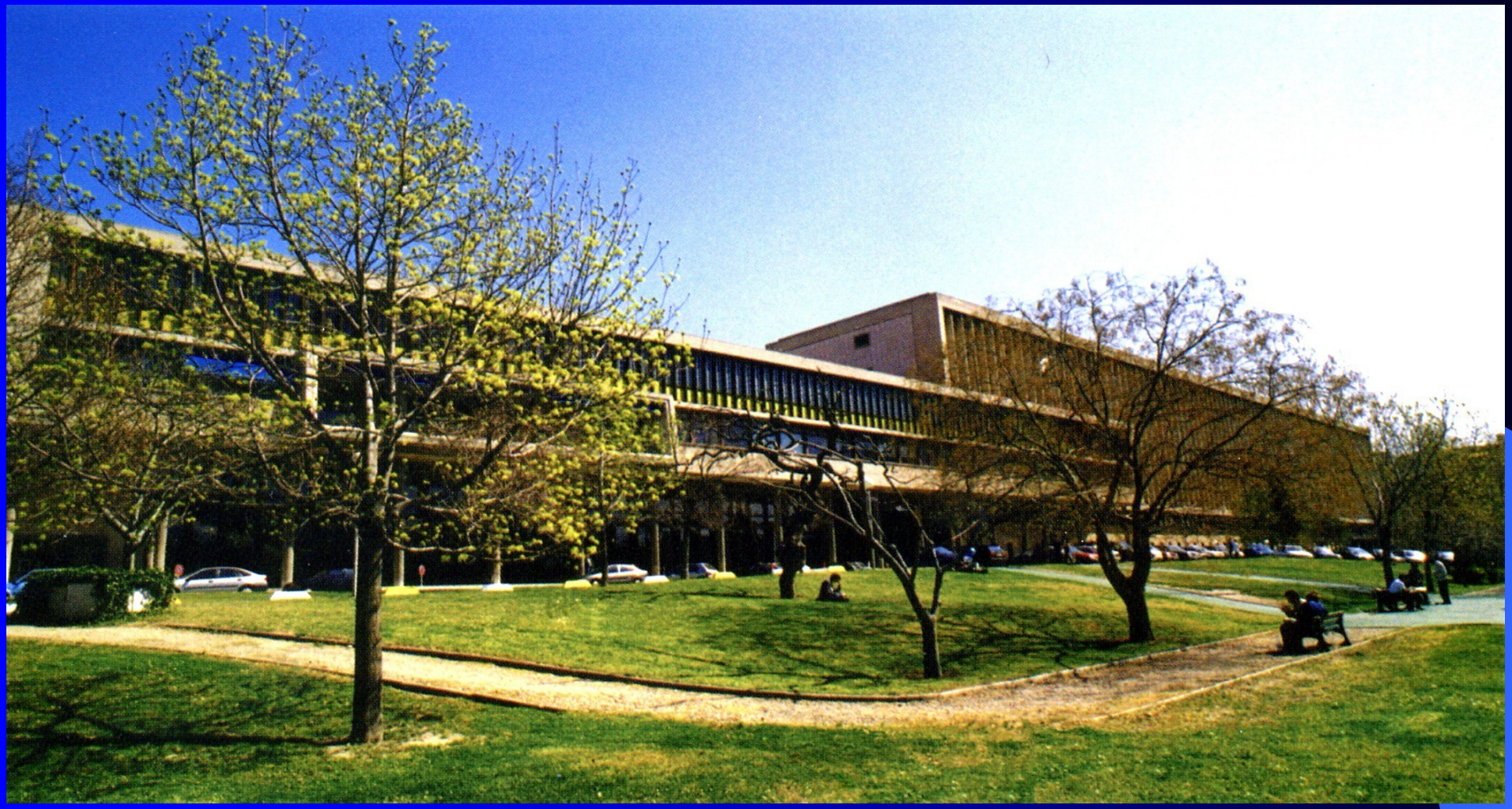
- Create a centre of excellence in molecular imaging technologies
- Recognized at the European level
- Build around 6 departments
  - Technological developments
  - Radio-tracers developments
  - Imaging for biology
  - Clinical applications
  - Education &training
  - Industry

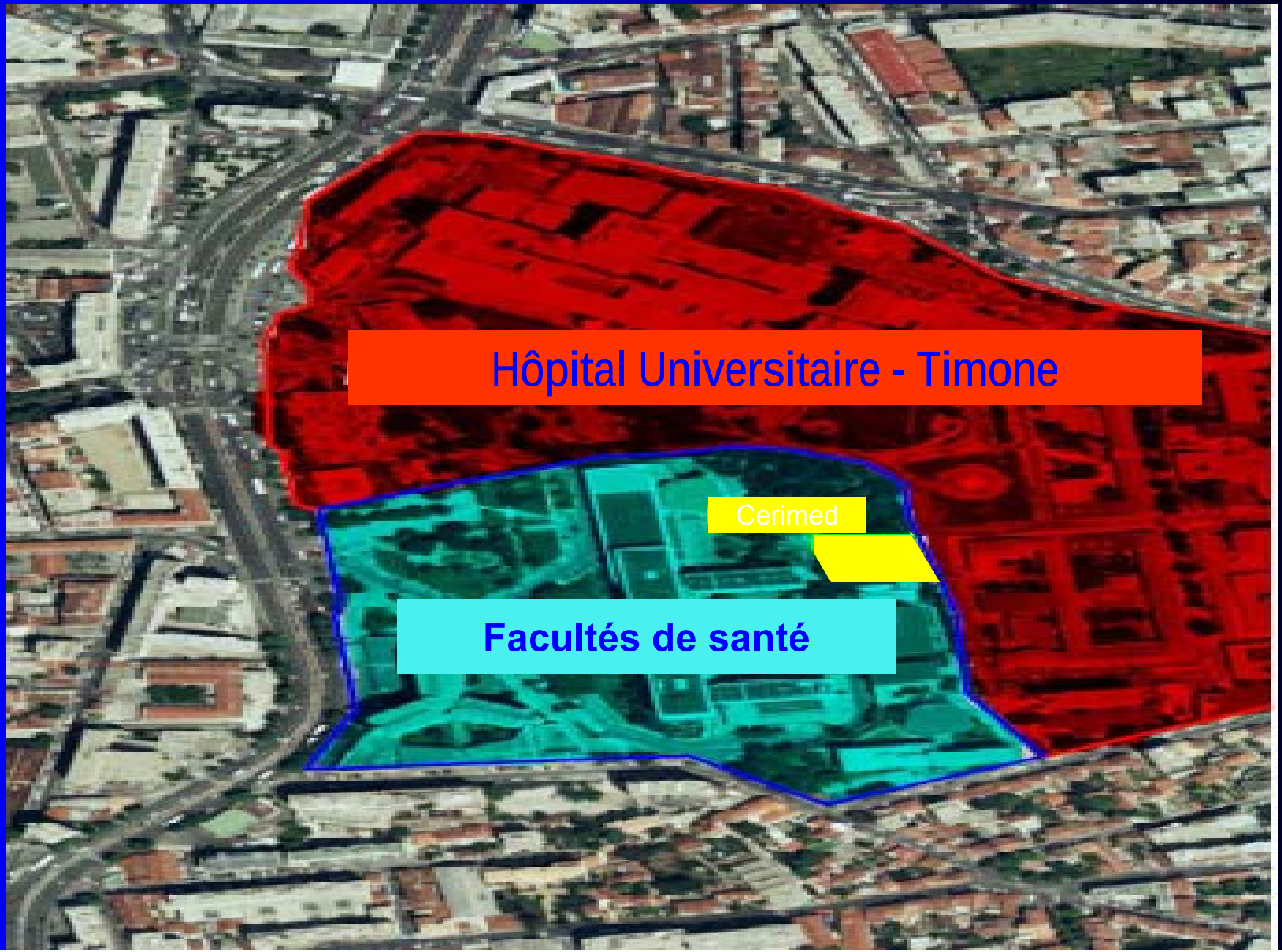
CERIMED in the world of imaging



Site

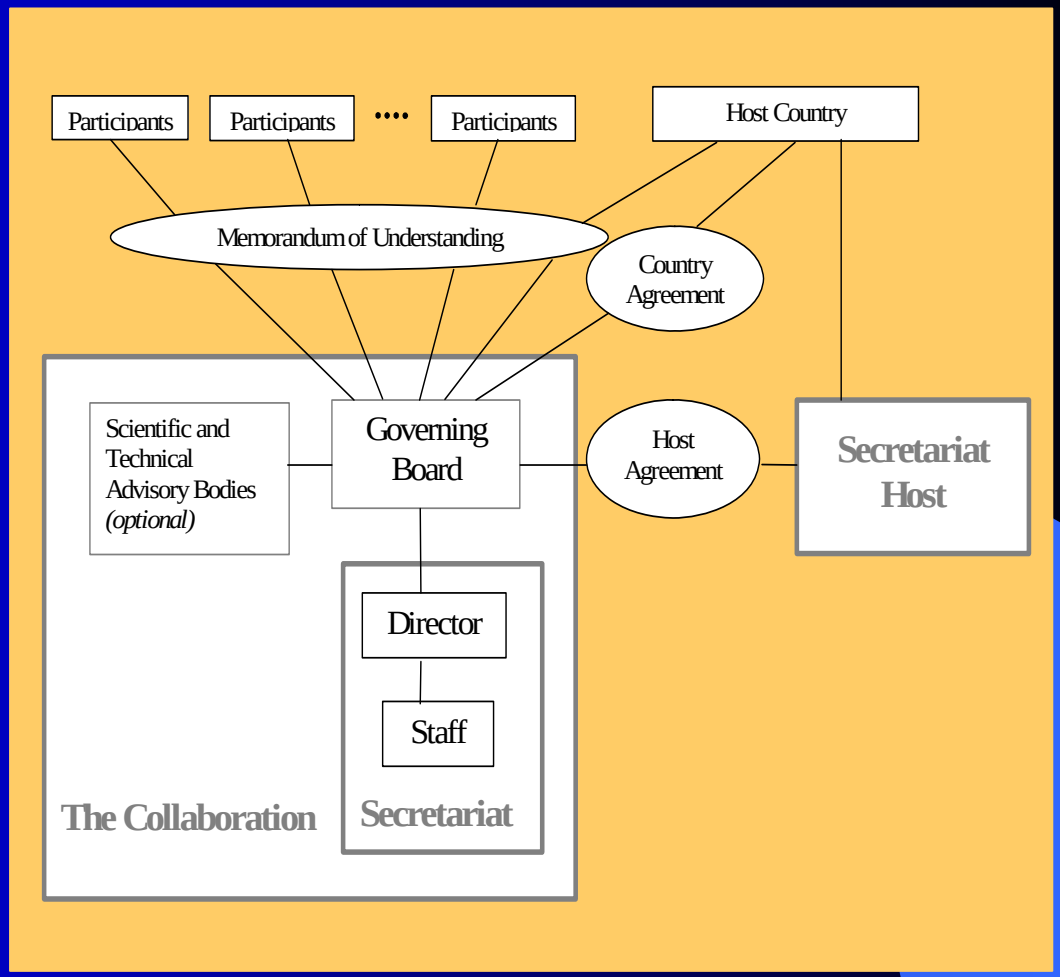

Clinical Validation Hall 200m²
Animal Validation Hall 150m²
Assembly Hall 250m²
Mechanical workshop
Optical lab
Electronics lab
Software lab
320m²
Cyclotron
Radiochemistry
500m² underground
Offices
Administration
Meeting Room
750m²
Library
cafeteria
230m²




Hôpital Universitaire - Timone
Cerimed
Facultés de santé

Proposed Organization

- Supra-institutional at the European level, based on OECD International Project Template
- Host country funding for infrastructure & running costs (including core manpower)
- Public/Private foundation for generic R&D (including manpower)
- Bilateral contracts for specific industry oriented R&D
- Rigorous IP management



Provisional structure

- On 9 Decembre 2004, in the frame of a concerted action between the french Ministry of Health and the Université de la Méditerranée in Marseille, the President of the University, Prof. Y. Berland has nominated

Prof. Charles Oliver

Councilor of the Président

CERIMED Project Leader

To setup the project in Marseille

Provisional structure

- In order to setup the CERIMED project in the best conditions, Prof. C. Oliver has defined a provisional structure to assist him, with:
  - A Medical Director, O. Mundler (CHU Timone, Marseille)
  - A Technical Director, P. Lecoq (CERN, Genève)
  - An Executive Committee
  - A Scientific Policy Committee

Executive Committee

- Mission: ***Take political actions and develop means for the setting-up and the international deployment of the project***

- Composition:
  - Chair — C. Oliver (Université de la Méditerranée)
  - Technical Director — P. Lecoq (CERN)
  - Medical Director — O. Mundler (CHU Timone)
  - Members — R. Aleksan (Directeur CPPM)
    V. Atger (Cancéropôle PACA)
    J. Boulesteix (Observatoire Marseille Provence, OPTITEC)
    C. Chagnaud (Radiologie, Université de la Méditerranée)
    J. Darcourt (PU-PH Biophysique et méd. nucléaire, Nice)
    J.P. Fabre (Directeur EGIM)
    M. Janier (Creatis-CERMEP, Lyon)
    P. Le Du (CEA-DAPNIA, Saclay)
    R. Rieu (ESIL, Chef du Département de Génie Biomédical)
    S. Tavernier (Univ. Libre Bruxelles, Spokesman CRYSTAL CLEAR)
    D. Townsend (Univ. of Tennessee, Knoxville, USA)

Scientific Policy Committee

www.cern.ch/cerimed/

- Mission:
  - ***Define the scientific contents of the project***
  - ***Evaluate the immediate and future needs in imaging for biology and medicine***
  - ***Define thematic actions and priorities for the development of technologies relevant for molecular imaging***

- Composition:
  - Co-chairs — P. Lecoq (CERN) — Technical Director
    O. Mundler (CHU Timone) — Medical Director
  - Ex officio member — C. Oliver (Univ. de la Méditerranée) — Project Leader
  - Members — L. Bidaut (M.D. Anderson Cancer Centre, Houston, USA)
    P. Cozzone (CHU Timone)
    P. Delpierre (CPPM)
    F. Flory (EGIM, OPTITEC)
    M. Hofmann (Hopital Insel, Berne)
    P. Mangeot (CEA-DAPNIA, Saclay)
    S. Mensah (CNRS-LMA)
    C. Morel (Université de la Méditerranée, CRYSTAL CLEAR)
    J. Pailhous (IFR E.J. Marey, Marseille)
    T. Pourcher (CEA Unité TIRO, Nice)
    D. Sappey-Marinier (Creatis, Lyon)

European Deployment Group

- On Jan 11, 2006 the executive committee decided to setup a European Deployment Group, directly linked to the executive committee

- Mission:
  - ***Promote Cerimed action in Europe***
  - ***Identify existing structures and promote partnerships with Cerimed***
  - ***Prepare collaboration protocols at the highest administrative and political levels***
  - ***Involve at the earliest stage european collaborators in the Cerimed managerial structure***

- Composition:
  - ***Chairman: D. Townsend***
  - ***One high level representative from each country (political and scientific)***

This group could be the seed of the future Cerimed European Council in charge of the management of Cerimed

Cerimed Today

- The French infrastructure plan (2007-2013) recently approved the setting-up of Cerimed infrastructure in Marseille (25M€)
  - Operational for Mid 2009
- 3 pilots projects approved and funded
  - TomoX/Gamma on small animal
  - ClearPEM-Sonic on mammography
  - Evaluation of Thyroïd nodules by elastography
- International events
  - EuroMedIm, May 2006, Marseille on Molecular Imaging
  - Workshop on DAQ, Marseille, 14-15 Sept 2005
  - Workshop on Vascular Imaging, Rome, 13-14 Nov 2005
  - Workshop on Breast Imaging, Marseille, 25 Jan 2007
  - Worshop on Stem Cells Imaging in preparation, mid 2007

Cerimed Today

- Networking several Universities an Engineering schools in Europe for a master interfacing Physics/Enginnering and Medicine/Biology
  - Discussions initiated with Marseille, Lyon, Milano, Rome
- Master Research Agreement with Siemens Medical Solutions
- Towards a proposal on multimodality imaging for the first call of FP7 (April 2007)

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

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Centre Européen de Recherche en Imagerie Médicale

European Centre for Research in Medical Imaging

TOF vs. Conventional PET

- *25 psec* time stamp for accurate data sampling

- contributors to ToF Timing Resolution of 650 psec:
  - Crystal 450 psec
  - PMTs 100 psec
  - Other 100 psec

- **electronics design plays a key role in preserving the timing resolution**