

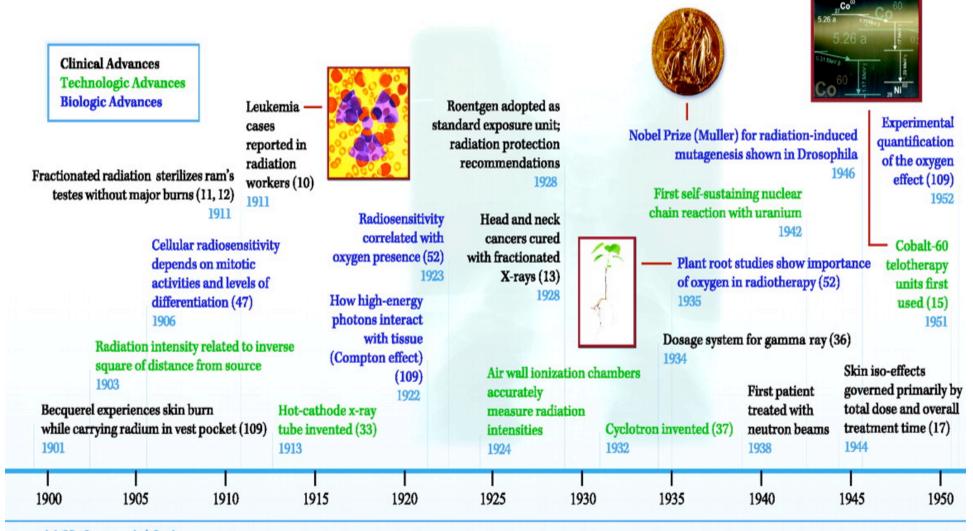
### Medical Applications from particle physics

Manjit Dosanjh Advisor for Life Sciences, CERN



Manjit Dosanjh, APS 2010

#### Figure 2. Advances in Radiotherapy: 1900-Present



**AACR Centennial Series** 



I I 1955 196	i0 1965	l 1970	l 1975 19	I I 980 1985	1990	l 1995	1 2000	1 2005	l 2010	
First patient treat proton beams (at 1954			sk from exposure <i>in utero</i> (109)	Development of D	ART (40) disco 1988		array techno nan genes (1)	logy to study ex L6)	pression	
Hypoxia from limiting oxygen diffusion (53) 1955	demonstra 1963	l 1977 ivity Surviv ted (109) (109) 1971	2 al curves for norma	1985 al bone marrow	Nucleotron produces first computer-cont afterloader 1985	1994 rolled SBRT to 1 1995	reat extracra	nial tumors (27,	28)	
curves for irradiated cells (49) 1956					tential doubling 1992 LDR and HDR brachytherapies					
Clonogenic survival	(at Harvard/MGH		t for IMRT (42) 1978	1980 Iso-6	0000					
amage repair shown (109) 1959	in brachytherapy 1961	Metronidazole hypoxic cell sensit		Model sugges occurs before primary tumo		. 1991	-	nce of the huma e completed (1)		
Cellular radiation	diation after-loading	radiosurgery 1968		MRI clinically 1980			Cancer cell survival correlated with tumor control probablility after radiotherapy (21, 22)			
la l	<b>curve (19)</b> 1967	Gamma — knife for cranial		Multi-leaf collimators developed 1980						
	First in vivo radiation survival		A.	1980	alosensitivities (	of early vs. late respond	ling tissues ()	(12)		

Cancer Research



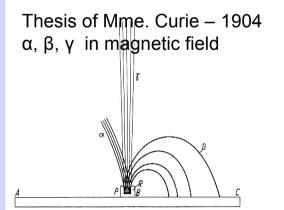


### .....beginning of medical physics

Henri Becquerel

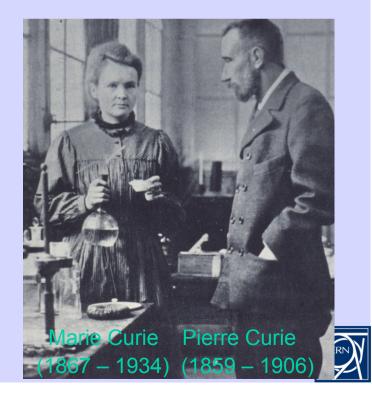
1896: Discovery of natural radioactivity 10 - 1000 96. Salfah Dubl D'urang & d.D. Pol. Papier sois - Carig De Carine Inines -Expense an Able le 27. de arte Care Selfra le 16. inlefter le 1° mars.





1898: Discovery of radium

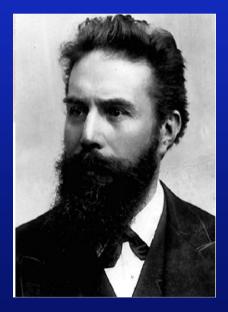
used immediately for "Brachytherapy"



### 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



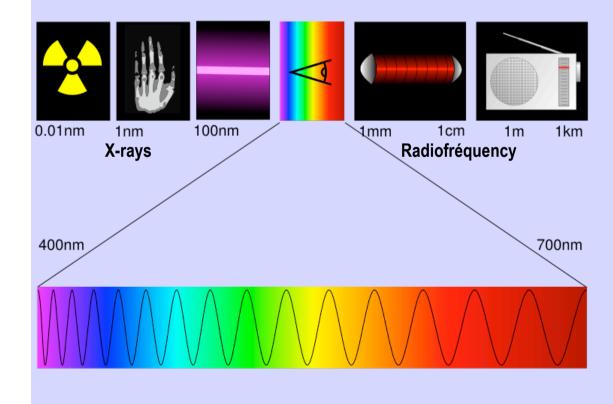
### Röntgen received the <u>first</u>Nobel prize in <u>physics</u> in 1901



Manjit Dosanjh, APS 2010

# History: Discovery of X-rays

- •Since 1895, inventor Wilhelm Rötgen
- •EM wave, with energy range: 30 -100 keV
  •From film to digital devices





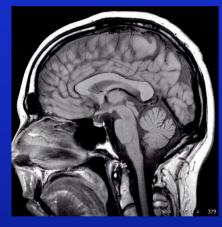


### MRI, Magnetic Resonance Imaging



Felix Bloch Physicist Stanford

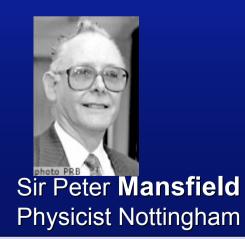
#### **The Nobel Prize in Physics 1952**

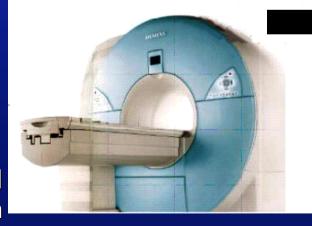


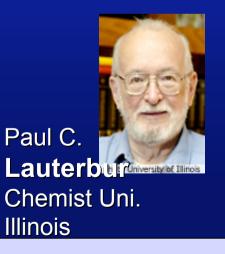


Edward M. Purcell Physicist Harvard

### The Nobel Prize in Physiology or Medicine 2003



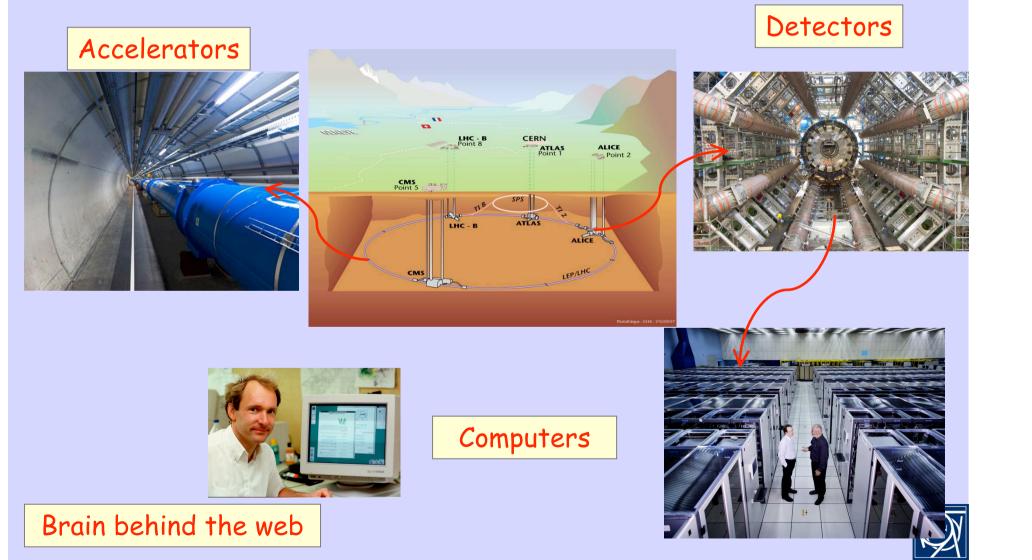






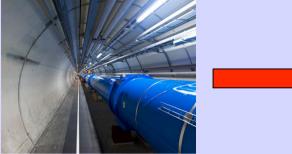
**Physics Teachers** 

# The tools of the trade .....



# **Medical Applications**

Particle beams for cancer treatment





Particle detector technologies for medical imaging





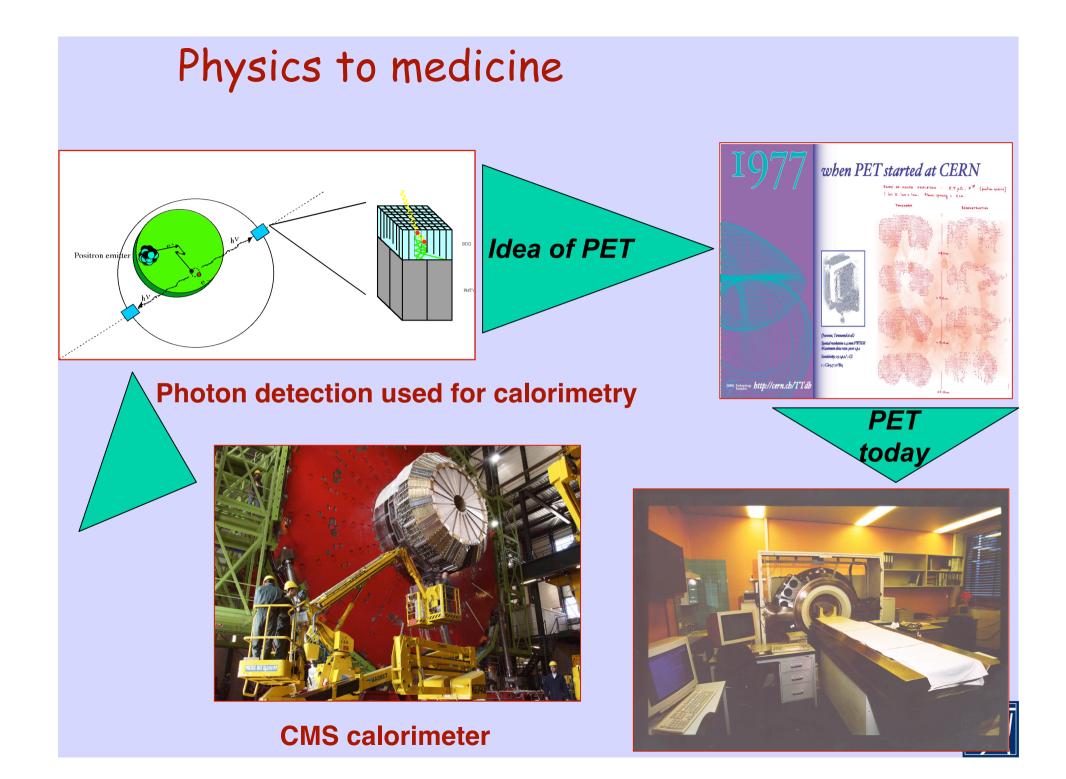
Grid computing for medical data management and analysis





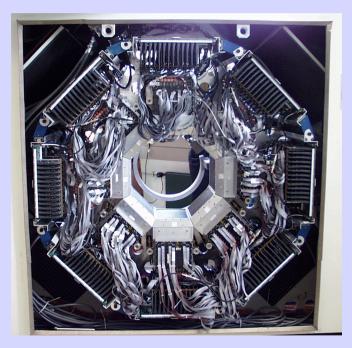






# Similar challenges detectors

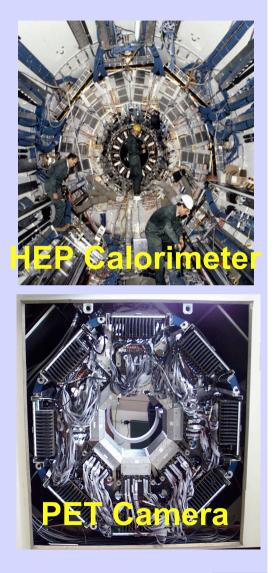






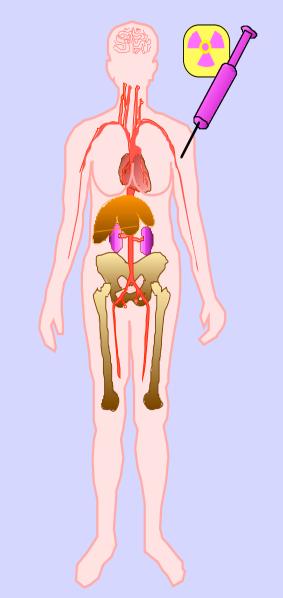
### Similar challenges for PET and HEP detectors

- New scintillating crystals and detection materials
- Compact photo-detectors
- Highly integrated and low noise electronics
- High level of parallelism and event filtering algorithms in DAQ
- Modern and modular simulation software using worldwide recognized standards (GATE)





# Inject Patient with Radioactive Drug

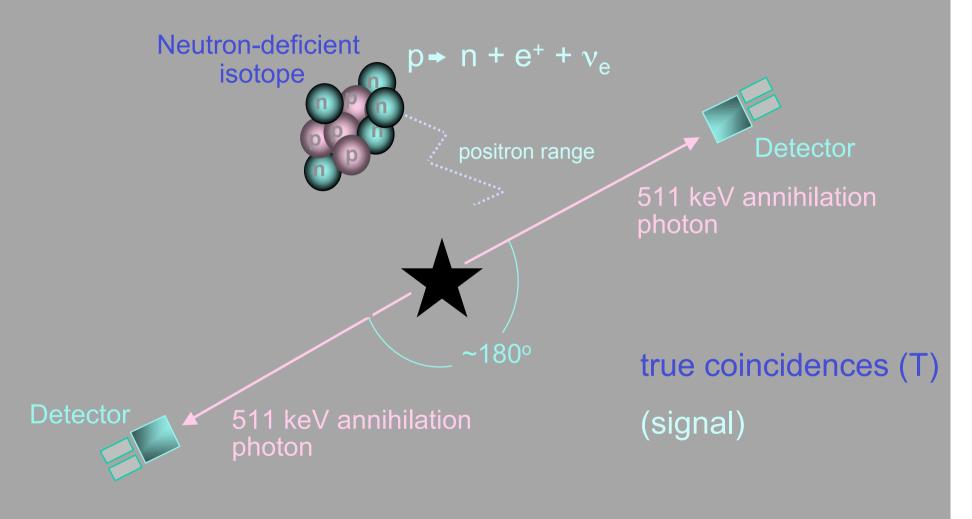


- Drug is labeled with positron (β<sup>+</sup>) emitting radionuclide.
- Drug localizes in patient according to metabolic properties of that drug.
- Trace (pico-molar) quantities of drug are sufficient.
- Radiation dose fairly small (<1 rem).

# Drug Distributes in Body



# PET: true events







# Crystal Clear Collaboration

-New scintillators :

- LuAP, phoswich LuAP-LSO (CERN patent)
- other crystals
- new photodetectors (Avalanche PhotoDiodes)

-new low noise front end electronics

-new intelligent DAQ systems with pipeline and parallelized architecture

- -better simulation GEANT 4
- -- better reconstruction algorithms



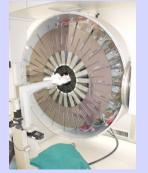
The ClearPET LYSO/LuYAP Phoswich Scanner A high Performance Small Animal PET System Higher e





#### The Design

•20 detector cassettes on the ring
•each cassette has 4 PM in line
•each PM has 64 photocathodes
•each photocathode reads 1 phoswich
•each phoswich has 2 crystals LYSO and LuYAP
•each crystal is 2 x 2 x 10mm<sup>3</sup>
•open gantry diameter adjustable 120 - 240mm
•rotation 360 degree
T cosine resolution 2 ns FWHN
Spatial resolution 1.5 mm at centre
Peak sensitivity >4%





### Introduction: Breast Cancer

- 1 women in 8 will develop cancer throughout her life
- 2<sup>nd</sup> cause of cancer death amongst women
- Very good survival rates if detected at an early stage (> 75% of patients have a 10-yr disease-free survival if tumor < 5cm)</li>
- $\rightarrow$  Breast cancer screening is now standard technique:
- Palpation: low sensitivity and specificity
- X-ray Mammography: high sensitivity and specificity BUT less reliable for dense breasts, unsuited for young, pregnant women and implants
- Ultrasound: complementary to X-ray
- Biopsy: only to confirm previous indication
- MRI: very high sensitivity BUT low specificity and high costs
- Whole-body PET: only technique with metabolic information BUT low resolution and high costs
- $\rightarrow$  Room for a new technique

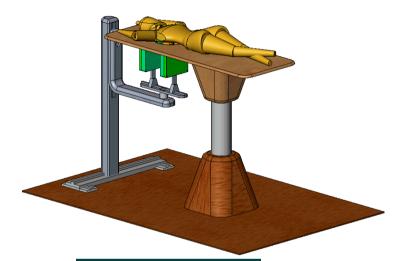


The Pink Ribbon – the international sign for breast cancer awareness



# Positron Emission Mammography CRYSTAL CLEAR Collaboration

#### Model of the PEM detector



Dedicated breast PET detector allowing high sensitivity to the small tumor detection

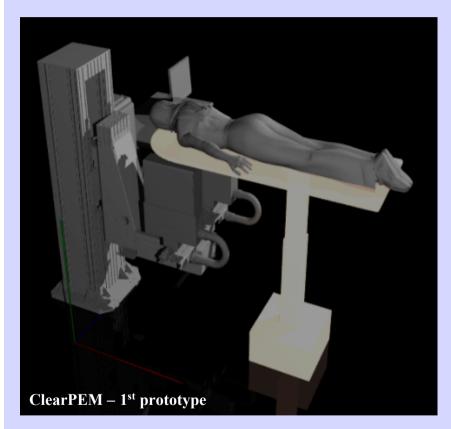
- Spatial resolution 1-2 mm
- High counting sensitivity
- Short PET exams
- Compatible X-Ray mammography
- Compatible stereotactic biopsy

#### **Technical characteristics:**

- 6000 crystals 2x2x20 mm
- Avalanche Photodiodes (APD)
- Low noise electronics
- High rate data acquisition
- Spatial resolution 1-2 mm
- Breast and axila region



# ClearPEM: The Project



- A dedicated mammography PET (Positron Emission Tomograph):
  - Breast exams with the patient in prone position
  - The plates rotate around the breast
  - PEM plates can be rotated for axillary exams

#### • Good spatial resolution : 1.4mm (FWHM)

- Fine crystal segmentation (2x2 mm)
- Reduced parallax effect by optimised depth of interaction resolution: 2 mm

#### • High Sensitivity:

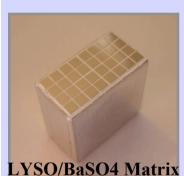
- Solid angle coverage as large as possible
- High photon interaction probability (20 mm long crystals)
- High efficiency due to good energy resolution at 511 keV: 15.9%

#### • Excellent Time Resolution:

- Single photon time resolution 1.5 ns (RMS)
- Coincidence window: 5.2 ns



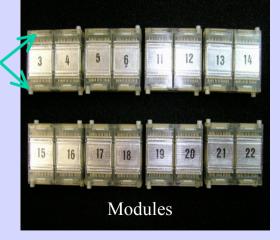
### ClearPEM: The Machine



APD array

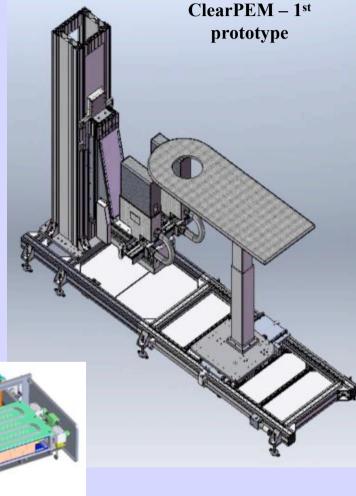
- 6144 LYSO:Ce crystals in 192 matrices
- APD readout on both sides of the crystal
- Fast Front-End readout with dedicated ASICs
- Two detector plates
- → 0.8MHz acquistion rate

Frontback readout





**Detector Plate** 



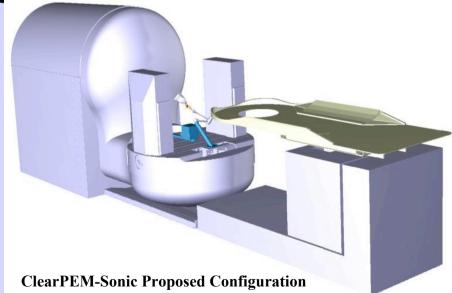


## Outlook

- Project status:
  - ClearPEM (Porto prototype): Phase 1 clinical trials ongoing
  - SuperSonic Imagine Aixplorer with 3D package : Clinical Trials ongoing / Commercial Release

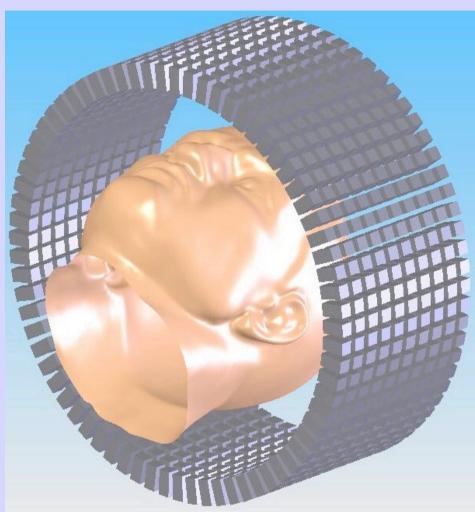
Spring 2010

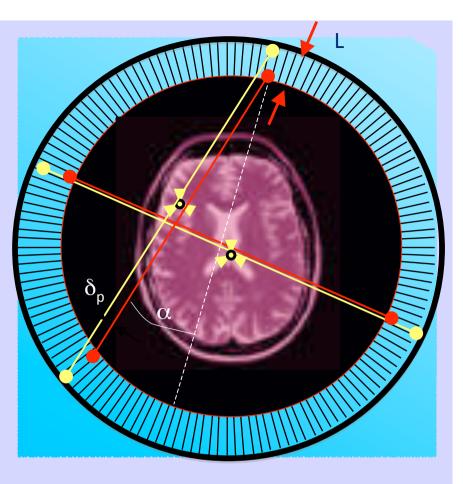
- ClearPEM-Sonic (installation at Hopital Nord, Marseille):
  - » Assembly well advanced
  - » Expected delivery: Spring 2010
  - » Expected Start of clinical trials: Summer 2010
- Possible further implementations:
  - Whole-breast 3D US imaging
  - Biopsy
  - SPECT





**Standard PET today** 





No DOI  $\rightarrow$  Parallax error  $\delta_p = L \cdot \sin \alpha$ 

- Short, radially oriented crystals
- readout in blocks by PMTs
- Anger logic decoding

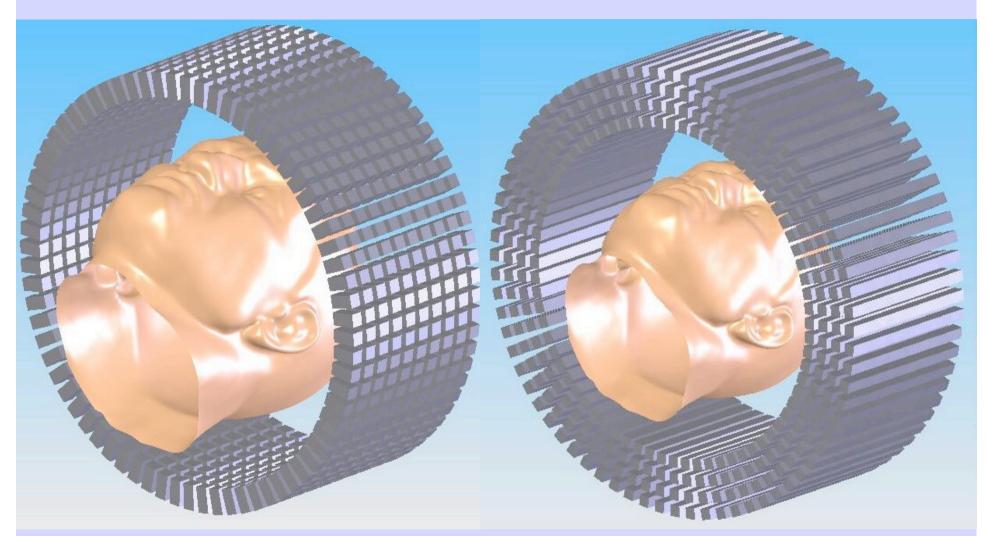
٠

• no depth of interaction (some exceptions) Physics For Health in Europe C. Joram Detection efficiency

$$\varepsilon_2 = \left(1 - e^{-\frac{L}{\lambda_a}}\right)^2$$

→ Find compromise between resolution and sensitivity 22

### **The AX-PET concept**



From short radially oriented, block readout crystals ...

# ... to long, axially oriented, individually readout crystals

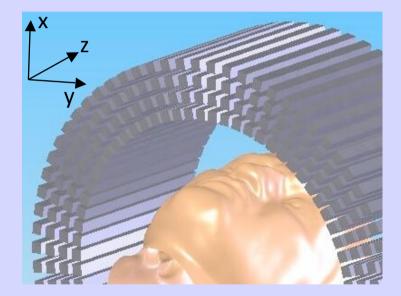


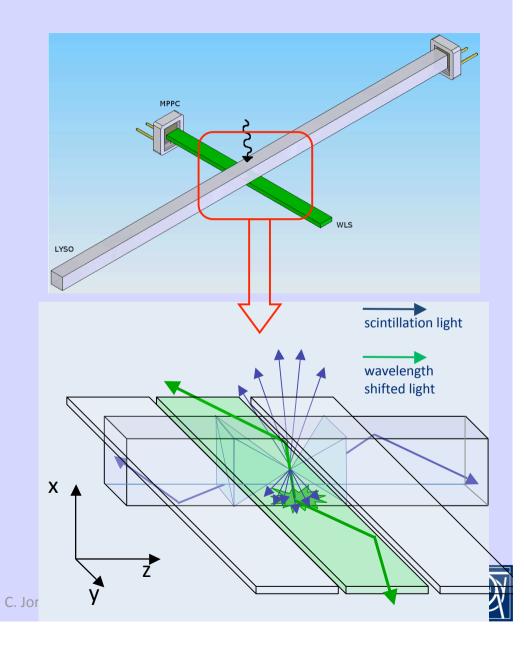
Physics For Health in Europe

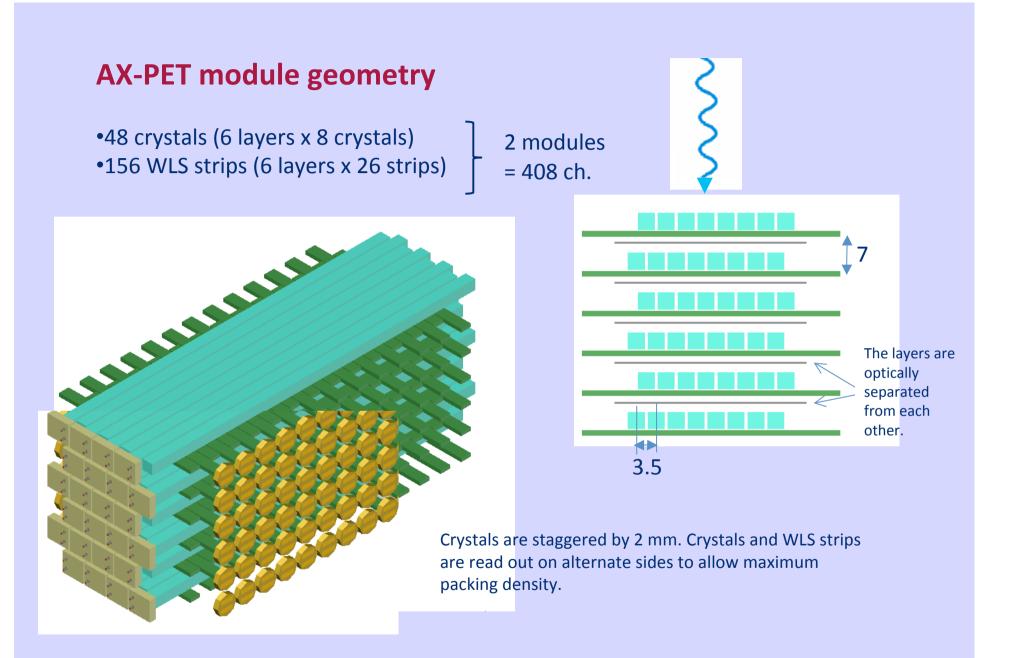
C. Joram

### **Our implementation of the AX-PET concept**

- How to read crystals ?
- How to measure axial coordinate ?



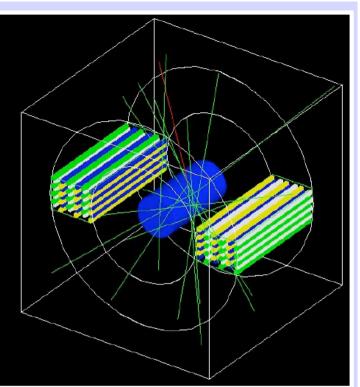


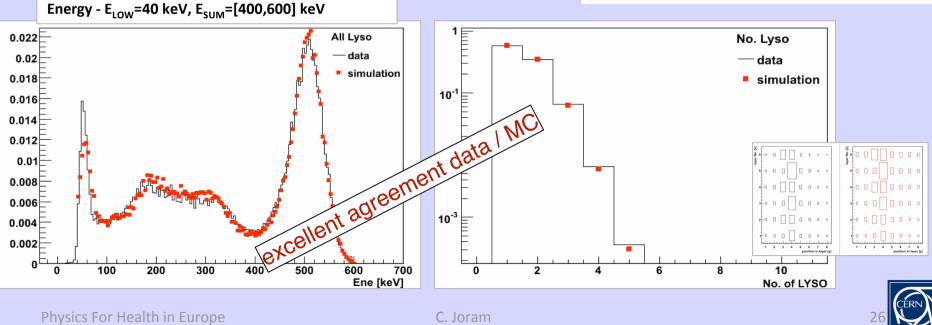




### **AX-PET simulation**

- **Geant4** (multi-purpose Monte Carlo tool, optical transport, dedicated geometry)
- **GATE** (PET dedicated MC, including time dependent phenomena, scanner rotation, source/phantoms...)





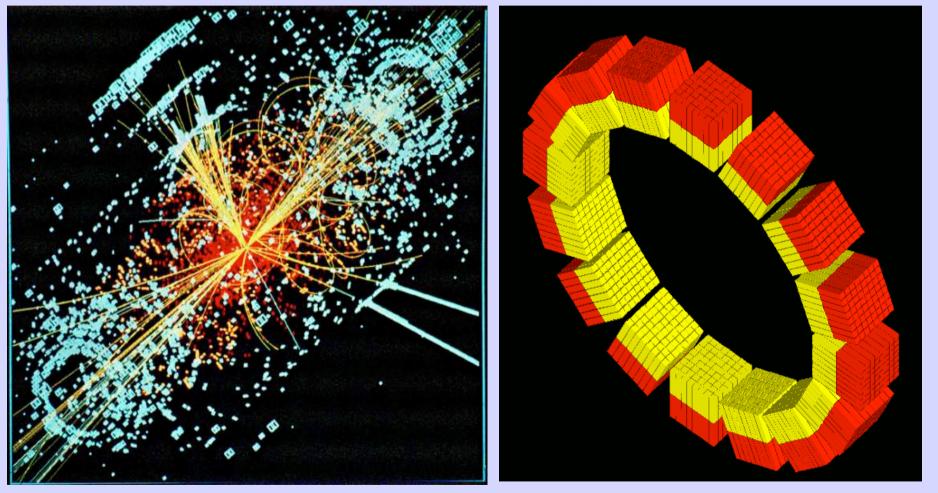
### **AX-PET main features**

- parallax-free 3D localization of photons.
- Spatial resolution (crystal and WLS strip dimensions) and sensitivity (additional layers) can be optimized independently. Physical limits in reach.
- The 3D capability should allow to identify a significant fraction of Compton interactions (Inter Crystal Scatter).
   ICS events can either be discarded (resolution fully maintained) or reconstructed (increased sensitivity).
- AX-PET concept can be scaled in size and number of layers to match specific needs.
   → small animal PET
  - → brain PET
  - → full body PET
  - → PEM (mammography)
- Concept and components are in principle MRI compatible and TOF extendable.



# Simulation

Higgs event at LHC (CMS) with Geant4 ClearPET with GATE: Geant4 Application for Tomographic Emission





### Task

Physics models of the Monte Carlo codes have to be validated and improved to respond to the high demand in precision for a very selected region of projectile-target combinations and energies relevant for ion therapy.

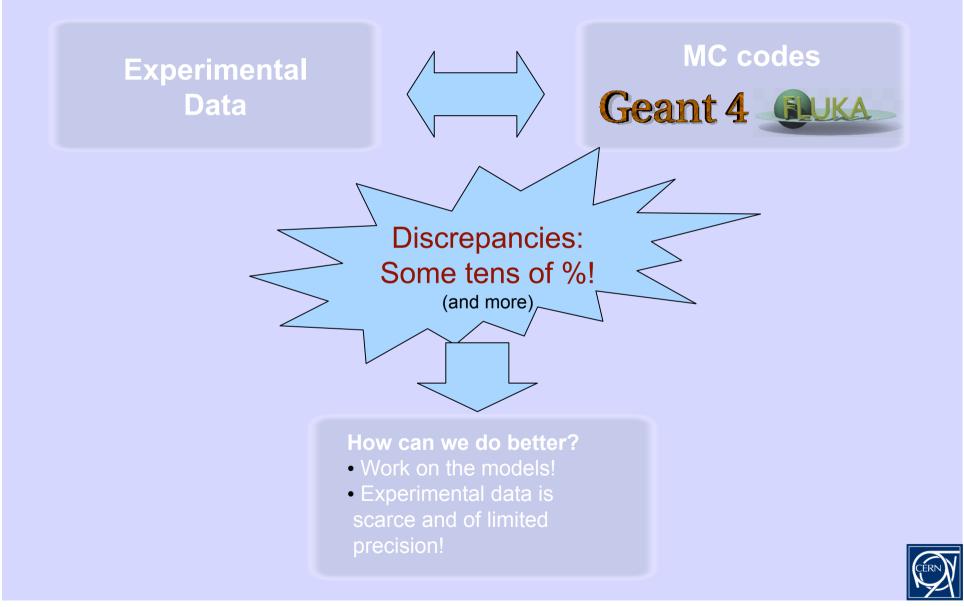
Monte Carlo particle transport systems developed at CERN:





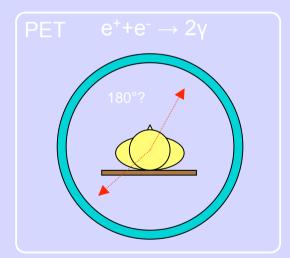


### Hadronic Models: How accurate are they for ion therapy?



# Modelling of Acollinearity for PET

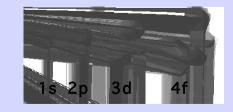
PET can be used to do dose monitoring for hadron therapy. A model describing acollinearity of the annihilation photons is being developed.



#### Model approach:

 Calculating probability for annihilation on different shells and valence band

 Taking in account momentum distribution of atomic orbitals!





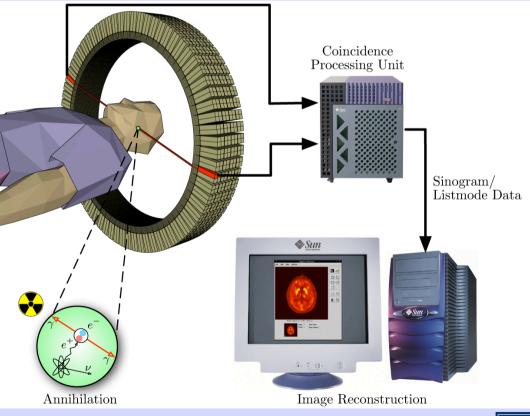
### Medical Imaging - PET (Positron Emission Tomography)

#### **Functional Analysis**

The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule.

Images of tracer concentration in 3-dimensional space within the body are then reconstructed by computer analysis.

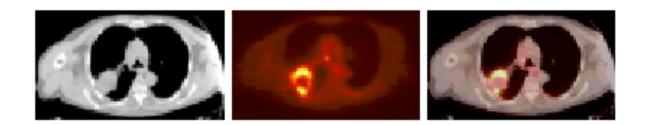
Crystals developed for LHC detectors are used in PET Scanners.



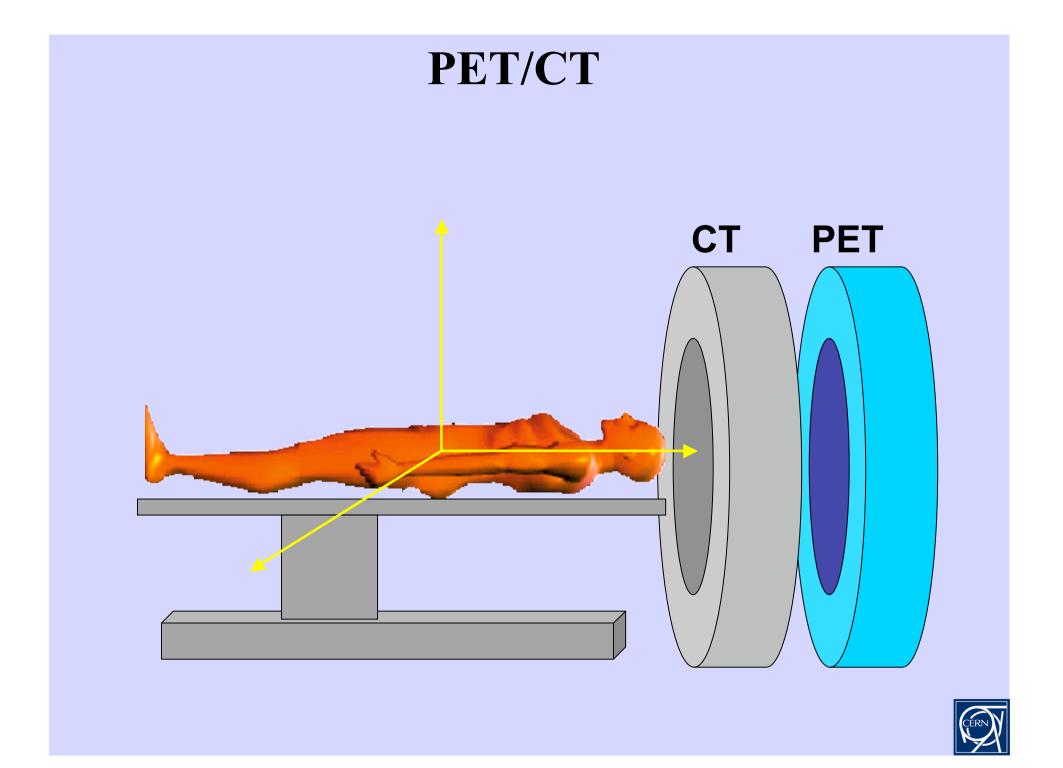


# Multi-modality imaging

Primary lung cancer imaged with the Dual/Commercial scanner. A large lung tumor, which appears on CT as a uniformly attenuating hypodense mass, has a rim of FDG activity and a necrotic center revealed by PET.







# A changing tide: digital imaging

### Current

- Limited contrast
- High dose
  - Restricted screening
  - Limited access to preventive health care

## Digital

- High contrast
- Lower dose
  - Opportunity for screening
  - Access to preventive health care



### IMAGING WITH THE MEDIPIX CHIPS

M. Campbell CERN Geneva, Switzerland 8 June 2010 Imaging 2010, Stockholm



#### What is Medipix?

The Medipix is an electronic chip similar to the electronic imaging chip in a digital camera. One difference is that the Medipix chip is sensitive to xrays instead of visible light. What is unique about the Medipix chip is that it can create the first true colour images with x-rays. Thus, it permits us to move from black and white x-ray images to full colour xray images. The chip also can be read out very rapidly. This allows the use the chip for colour x-ray digital movies or for fast colour x-ray CT scans





#### **Bio-medical applications of CERN technologies**

#### MEDIPIX2

Ga-As array detector bump bonded on a digital Silicon counter especially developed for X-rays Radiography

High Energy Physics original development: Particle track detectors X-ray gun

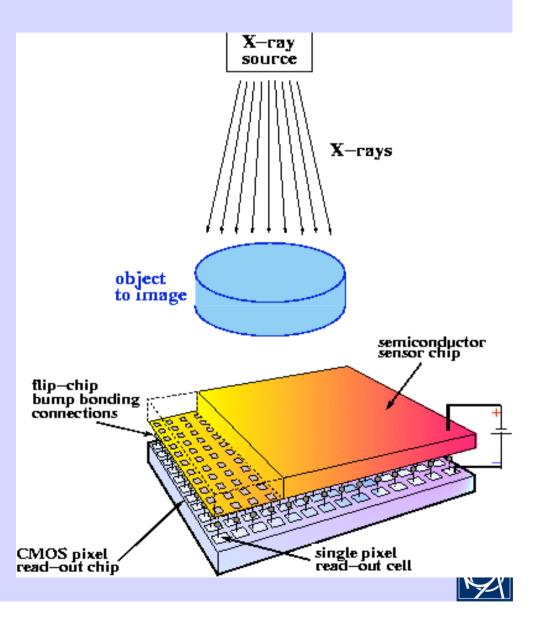
Main properties: Fully digital device Very high space resolution over small areas Very fast photon counting Good conversion efficiency of low energy X-rays Main technologies involved: Micro-electronics 0.25 mm C-MOS technology Flip chip technology Smart electronics

Status of the project: Design of MEDIPIX2 based on successful MEDIPIX chip in progress

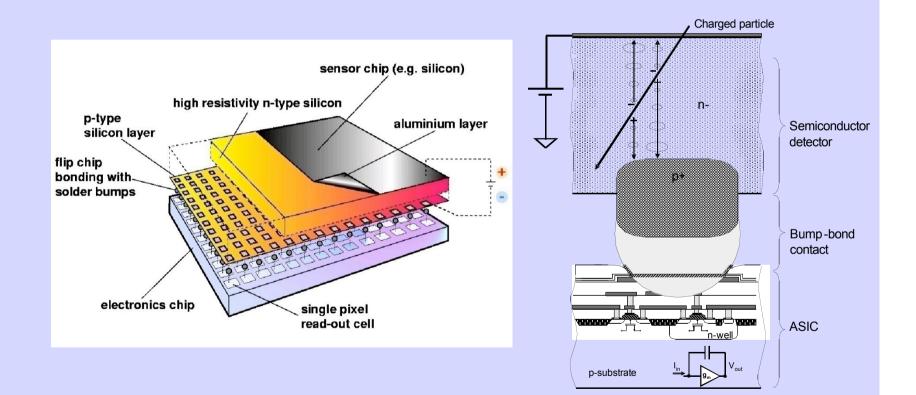


**MEDIPIX**: Allows counting of single photons in contrast to traditional charge integrating devices like film or CCD

- High Energy Physics
   original development:
   Particle track detectors
- Main properties:
   Fully digital device
   Very high space resolution
   Very fast photon counting
   Good conversion efficiency of
   low energy X-rays



### Hybrid-Pixel Detectors





### 'Imaging' in High Energy Physics - Summary

- Hybrid pixels offer simultaneously:
  - Practically noise free images
  - Fast 'shutter' times
  - On pixel event selection
- Hybrid pixels have been used as vertex tracking detectors
  - Extremely good pattern recognition performance
  - Modest material budget
- Hybrid pixels have been used as photon RICH detectors
  - Very high pattern recognition performance



### Medipix2 chip developments

- Chip designed in same CMOS technology as Alice and LHCb
- Pixel shape now square 55µm pitch
- Matrix of 256 x 256 pixels
- In-pixel counter with 'camera' logic
  - Externally applied shutter
  - Window discriminator
  - 14-bit counter with stop at 12000
- Very high flux capability
  - ≥ 3 GHits/cm<sup>2</sup>
- Frame-based readout
  - All bits read out in serial (5ms @ 200MHz) or parallel (300 $\mu s$  @ 100MHz)



### Use of Accelerators for cancer treatment



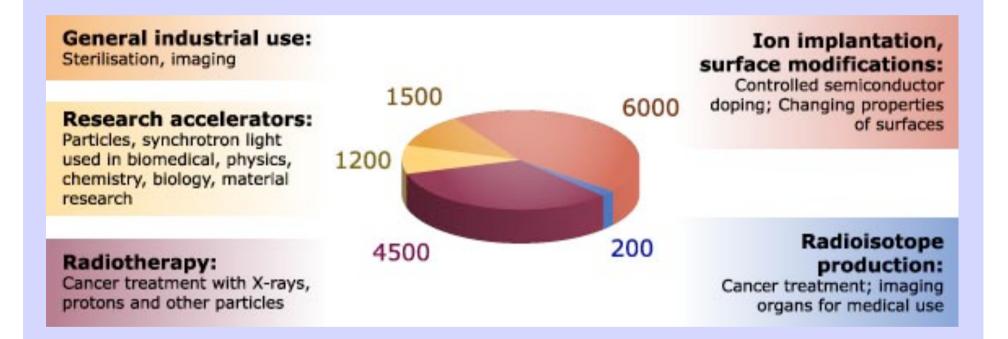
### Accelerators: developed in physics labs are used in hospitals



Around 9000 of the 17000 accelerators operating in the World today are used for medicine.



### Use of Accelerators Today





### The Problem

#### Cancer Incidence

- Every year about 2 million new cases in Europe
- The rate of patients treated with RT will likely increase in the years to come
- The main cause of death between the ages of 45 and 65.
   Second most common cause of death



### Cancer and Radiotherapy in 21st Century

- RT is, nowadays, the least expensive cancer treatment method (around 5% of cost)
- Good cure rate (30-40%)
- Conservative (non-invasive, fewer side effects)
- There is no substitute for RT in the near future

Present Limitation of RT: 30% of patients still fail locally after RT

(Acta Oncol, Suppl:6-7, 1996)

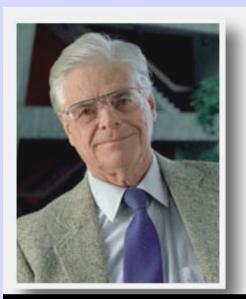


#### How to overcome failures?

- Physics & treatment technology: dose escalation
- Imaging: MRI, PET, image registration
- Biology: altered fractionation, radiosensitization

Raymond Miralbell, HUG

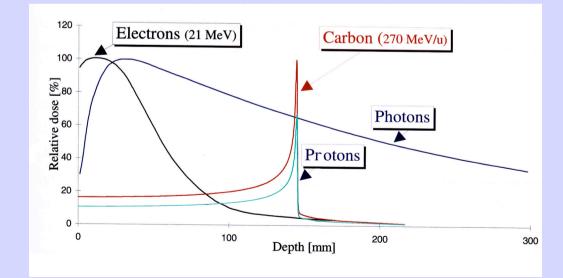




Founder and first director of Fermilab

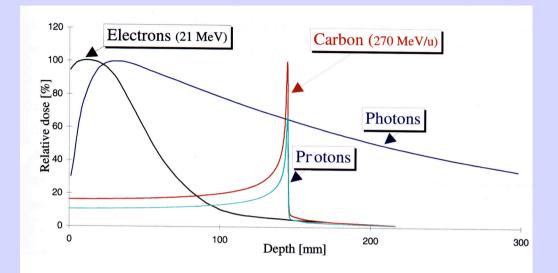
#### Hadrontherapy: all started in 1946

- In 1946 Robert Wilson:
  - Protons can be used clinically
  - Accelerators are available
  - Maximum radiation dose can be placed into the tumour
  - Proton therapy provides sparing of normal tissues





#### Hadrontherapy vs. radiotherapy



#### Photons and Electrons

- Physical dose high near surface
- DNA damage easily repaired
- Biological effect lower
- Need presence of oxygen
- Effect not localised

#### Tumours close to critical organs

- •Tumours in children
- Radio-resistant tumours

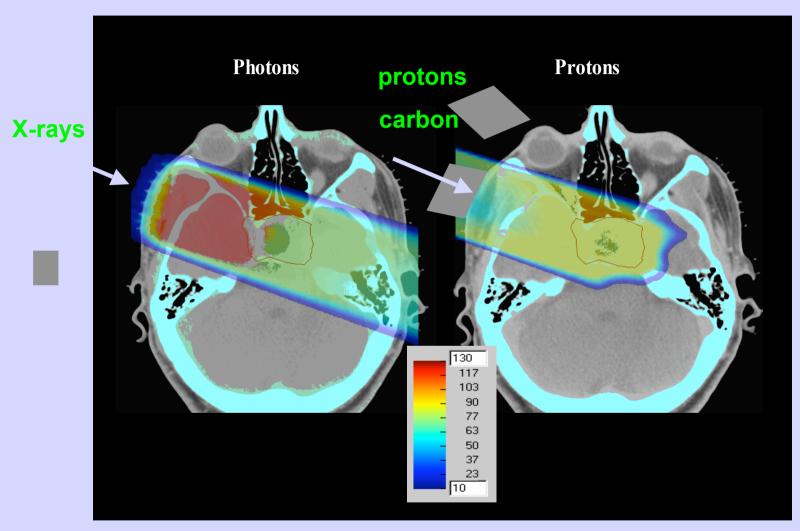
#### Hadrons

- Dose highest at Bragg Peak
- DNA damage not repaired
- Biological effect high
- Do not need oxygen
- Effect is localised



VS.

### Advantage of hadrontherapy





#### Main Parameters

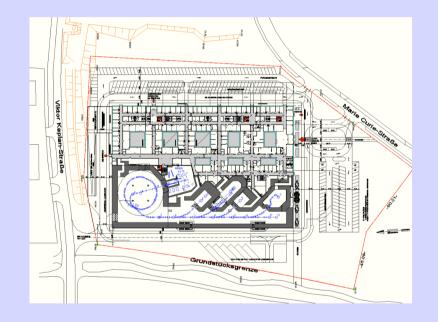
- Synchrotron based (C=76 m, cycle time > 1 second)
- Ion species: protons and carbon ions
  - Optionally and at a later stage other ions with q/m>1/3 are possible
- Energy range
  - Proton: 60-250 MeV (medical)
    - Higher proton energy provided for experimental physics: up to 800 MeV
  - Carbon: 120-400 MeV/n
- Intensities (maximum) in irradiation rooms
  - Proton: 1\*10<sup>10</sup> /cycle
  - Carbon: 4\*10<sup>8</sup> /cycle

### Tumour Therapy and Research Centre

MedAustron located in the north of Wiener Neustadt next to the future site of the new hospital

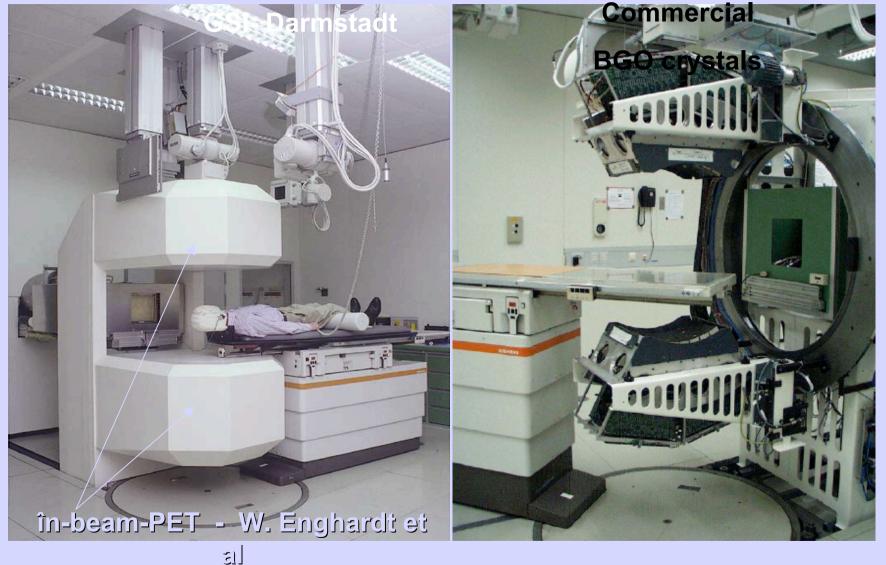
### **Applications**:

- Medical Treatment
  - Tumour treatment
  - Clinical research
- Non-clinical Research (NCR)
  - Medical Radiation Physics
  - Radiation biology
  - Experimental physics
- Accelerator operates 24/7.
- Beam time split Treatment: NCR about 50:50



M. Benedik

# In-beam-PET for range measurements with carbon ions

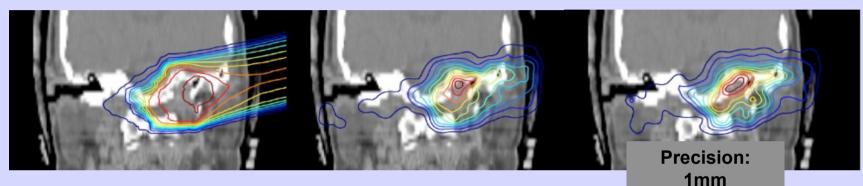




ICRT 09 - UA - 12.3.09

### Comparison with the data I

#### Chondrosarcoma of the skull base



Dose distribution (left) compared with the predicted (middle) and the measured (right) positron-activity distributions brought in 1999 to a

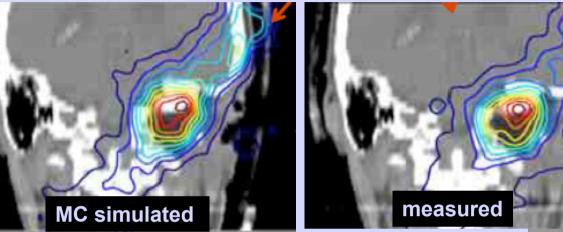


#### New calibration procedure of R(HU)



ICRT 09 - UA - 12.3.09

# In-beam-PET for Quality Assurance of treatments



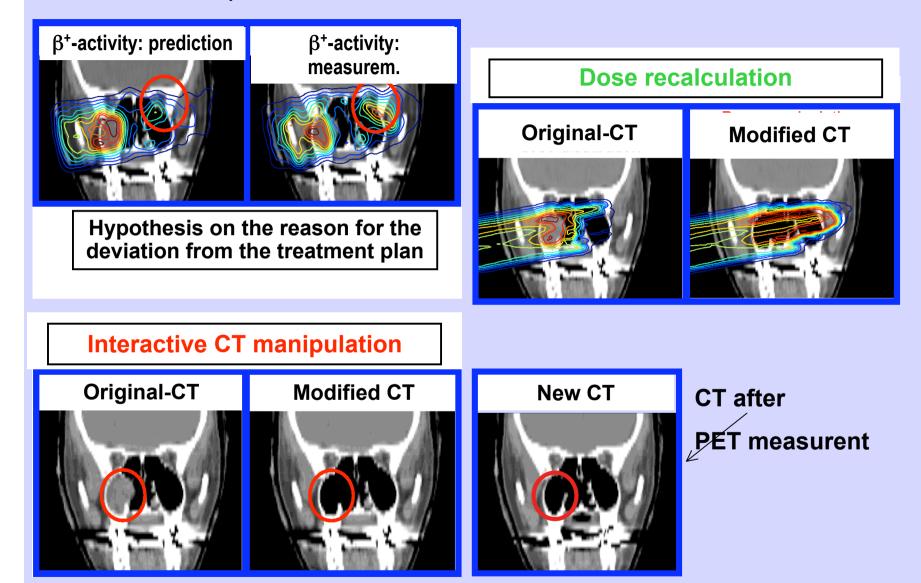
On-line determination of the dose delivered First time in 110 years!

Modelling of beta<sup>+</sup> emitters:

- Cross section
- Fragmentation cross section
- Prompt photon imaging
- Advance Monte Carlo codes

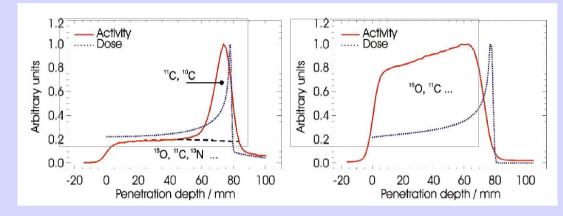


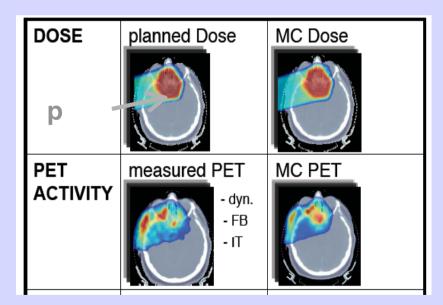
### Comparison with the data II





### The phenomenon is also induced by protons





Parodi et al "Patient study on in-vivo verification of beam delivery and range using PET/CT imaging after proton therapy" Int. Journal of Radiation Oncology, Biology, Physics 2007



### **MEDICAL IMAGING**

TECHNI	QUE	YEAR	ENERGY	PHYSICAL PROPERTY	IMAGING
RADIOLOGY	X RAYS IMAGING	1895	X RAYS	ABSORPTION	And Republics
ECHOGRAPHY	ULTRASOUND IMAGING	1950	US	REFLECTION TRANSMISSION	
NUCLEAR MEDICINE	RADIOISOTOPE IMAGING	1950	γ <b>RAYS</b>	RADIATION EMISSION	



### **COMPUTERIZED TOMOGRAPHY**

TECHNIQUE		YEAR	ENERGY	PHYSICAL PROPERTY	IMAGING	
X RAYS COMPUTERIZED TOMOGRAPHY	ст	1971	X RAYS	ABSORPTION		MORPHOLOGY
MAGNETIC RESONANCE IMAGING	MRI	1980	RADIO WAVES	MAGNETIC RESONANCE		MORPHOLOGY /FUNCTION
POSITRON EMISSION TOMOGRAPHY	PET	1973	γ <b>RAYS</b>	RADIATION EMISSION		FUNCTION



### Grids and e-health





# LHC data challenge

- 40 million collisions per second
- After filtering, 100 collisions of interest per second
- 10<sup>10</sup> collisions recorded each year
- ~10 Petabytes/year of data ~10 000 times the world annual book production, ~20km CD stack

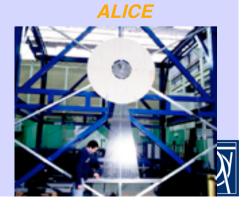


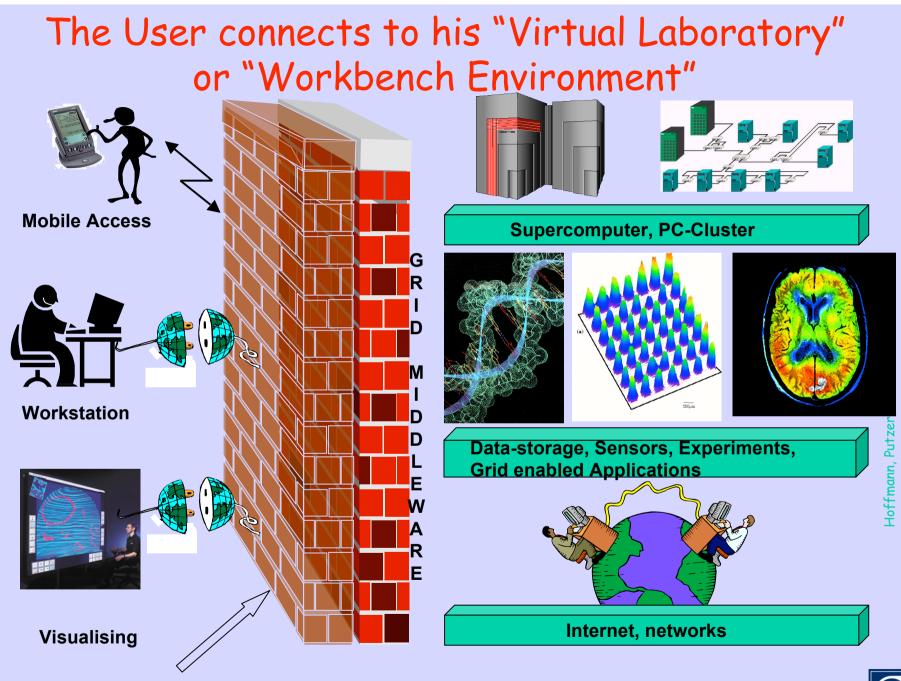














### MammoGrid Project

- To manage health care information for screening
- Acquisition of large sample of mammograms
- Standardization of mammograms
- Distributed data management system, cross-institute, cross-country queries
- Sharing of computing resources for the purpose of optimizing data storage and execution of computing-intensive algorithms\
- To assist health operators in their work environment and exchange data and practices



#### Lessons Learned from MammoGrid for Integrated Biomedical Solutions



CERN

From: David MANSET, CEO MAAT France, www.maat-g.com

### MammoGrid in Figures

#### Addenbrookes Hospital, UK

- 1423 patients

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- 9713 images total (4812 SMF)
- Associated data size : ~14 MB

#### • Udine Hospital, ITALY

- 1274 patients
- 17288 images total (8636 SMF)
- Associated data size: ~23.5 MB

~30'000 Images

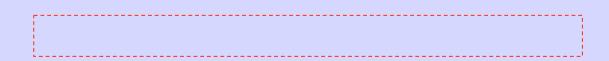


From: David MANSET, CEO MAAT France, www.maat-g.com

### Key Objectives

- Acquisition of *large sample* of mammogram images
- Standardization of mammograms (SMF)
- Annotation of mammograms by humans as well as CADe software
- Distributed data management system, cross-institute, cross-country
- Sharing of computing resources
  - Unlimited Storage
  - Computing-Intensive Algorithms

*Proof of concept* with active clinical participation







From: David MANSET, CEO MAAT France, <u>www.maat-g.com</u>

### **Technical Challenges**

• Make Grid *work in practice* and *usable* in hospitals

#### (clinician friendly)

 Investigate how the medical application can be isolated from the (still evolving) Grid as new Grid flavours emerge (e.g. OGSA→Web/Grid Services)

#### (grid friendly)

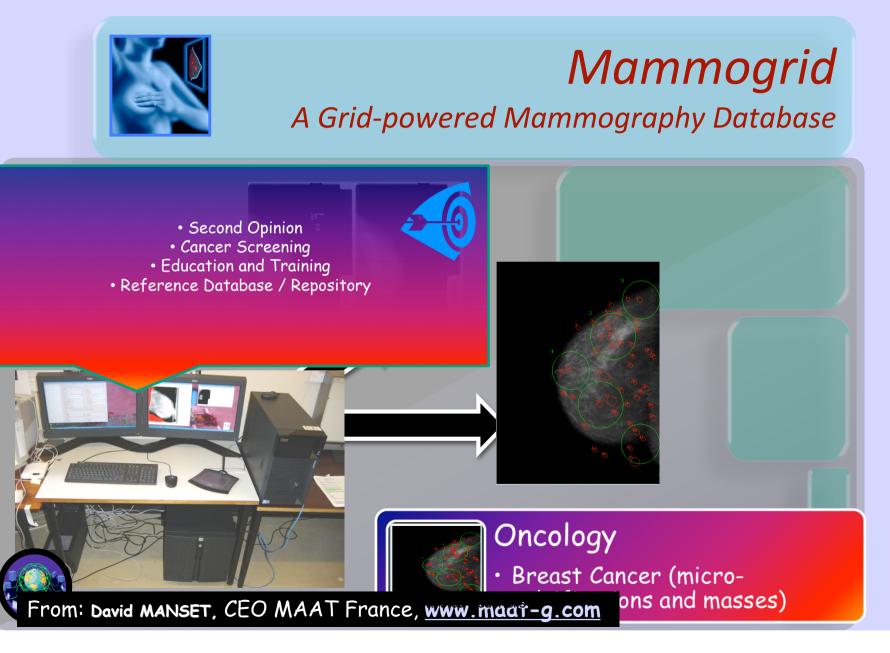
- Provide a distributed and federated clinical data management system
- Deliver a *secure system*, which can be integrated into a hospital information system



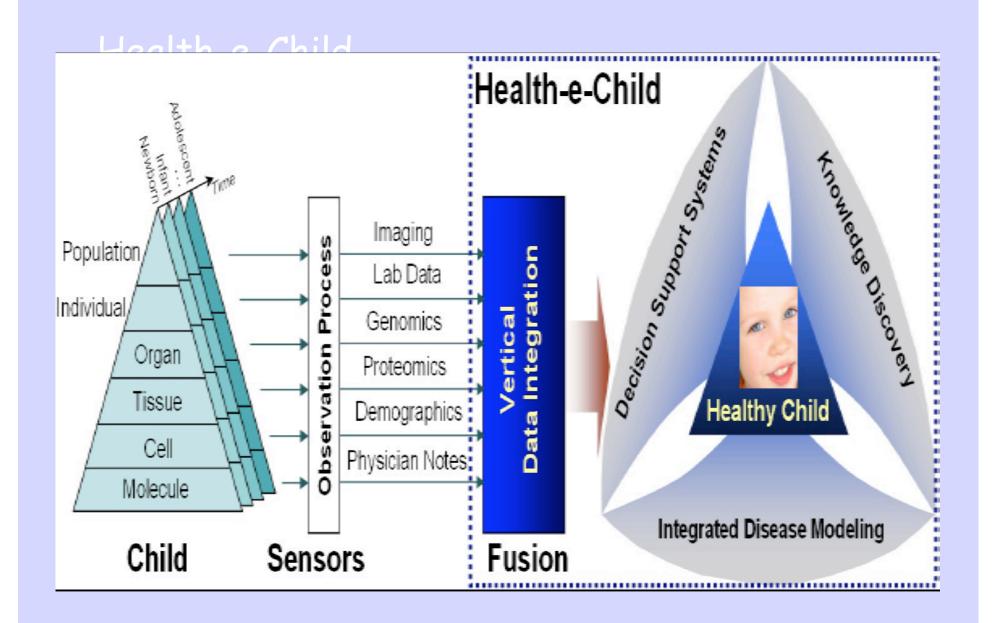


From: David MANSET, CEO MAAT France, <u>www.maat-g.com</u>

### Early example of health application on the grid







UWE HP Labs Presentation: 23<sup>th</sup> November 2007 FT om: Peter Bloodsworth, CCCS Research Centre, UWE, Bristol, UK, peter.bloodsworth@cer



## **Charged Particle Therapy Centres**

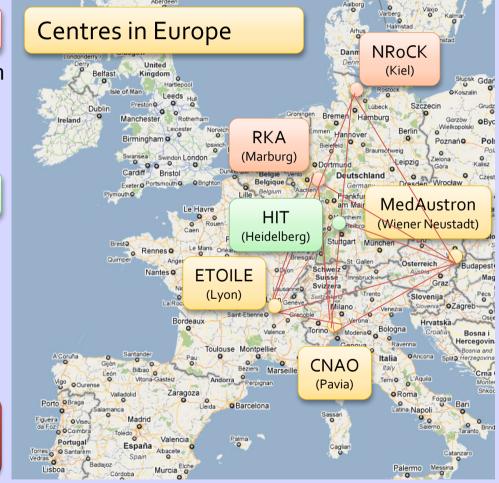
#### Protons

- use of protons proposed 1946 by R.Wilson
- first use on patients in 1954 (Berkeley)
- in 2009: >25 proton therapy centres

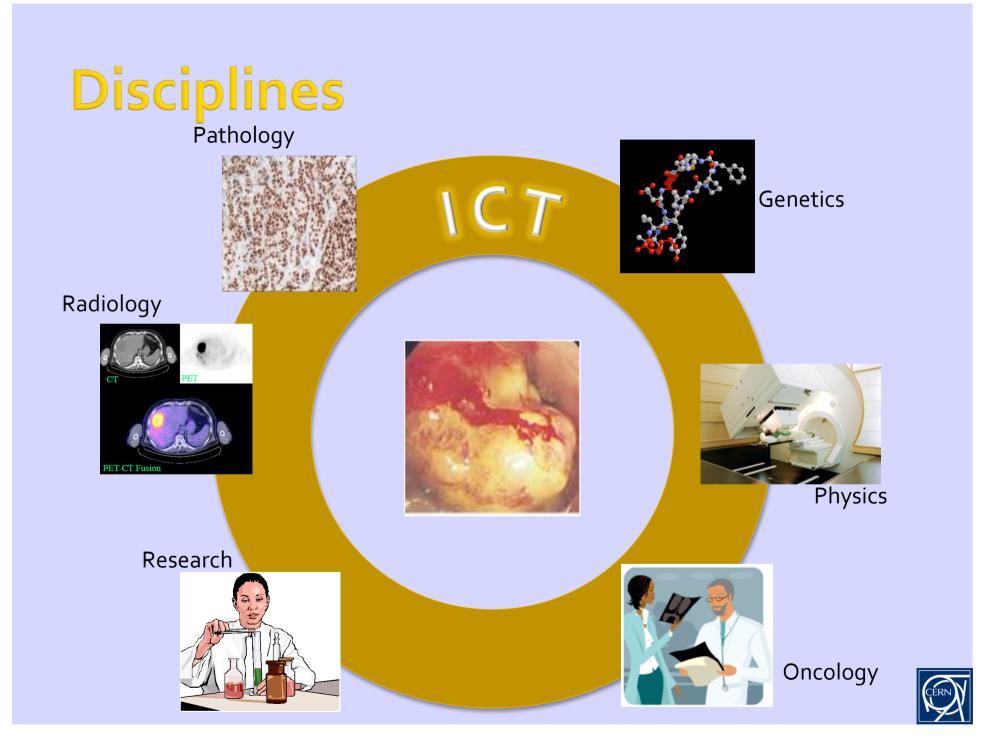
#### lons

- only 2 clinical centres using carbon ions (Japan) and physics research institutes until 2009/11
- HIT inaugurated in November 2009 •CNAO inaugurated in February 2010

Connect centres ... ... and make most of available data!



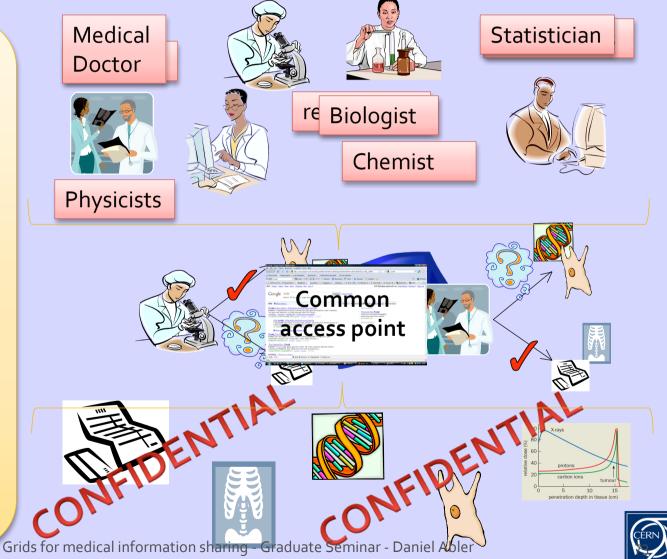




# Challenges

Platform for translational research and clinical practice (1/2)





# **Data standards and semantics**

- Heterogeneity
  - Different disciplines have different view on subject.
  - Different institutions have own measurement procedures and naming conventions
- Semantic Interoperability
  - Same meaning for sender and receiver
- Computer Interoperability





# **The Project**

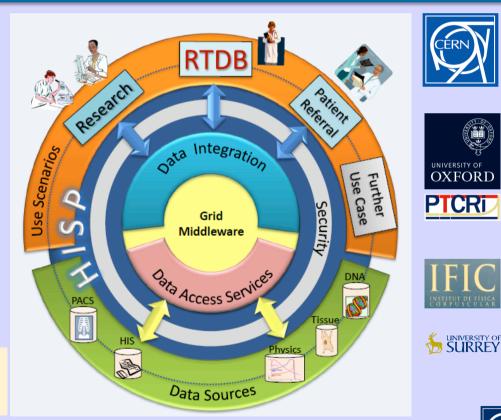
#### Prototype for a grid-based <u>Hadron Therapy</u> Information <u>Sharing</u> Platform (HISP)



- Technical Demonstrator
  - Scientific: Research Platform
  - Clinical: Patient Referral
- for follow-up projects
  - ULICE...

Abler, D.; Kanellopoulos, V. & Roman, F. L.

Future information sharing in Hadron Therapy





https://espace.cern.ch/partnersite/workspace/abler/Shared%2oDocuments/ConferencePoster/PARTNER\_Grid\_PosterAndA bstract\_PhysicsForHealthCERN2010.pdf

Poster at 'Physics for Health in Europe' workshop, 2-4 Feb. 2010, CERN, Geneva

24/06/2010

Information Sharing System for CPT - 1st year interview - Daniel Abler

# **Services in HISP**

#### Authentication

• log-in

#### Agreement Brokerage

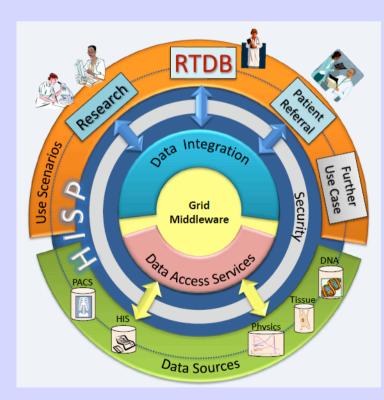
- contracts
- negotiation
- proposal submission

#### Data Analysis

- workflow design
- job manager
- execution

#### **Data Access**

- query
- transformation
- anonymisation
- visualisation
- export
- registration



#### Authorisation

- general and
- custom roles
- delegation

#### **Data Import**

- upload
- consistency check
- registration

#### Meta Data

- CDE registration
- curation
- data annotation
- browsing
- mapping



Information Sharing System for CPT - 1st year interview - Daniel Abler

