Abstract for OIST mini symposium
“New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015

Title: “BNCT as a new generation charged particle therapy - From Reactor to Accelerator –”

by: Director Akira MATSUMURA, University of Tsukuba Hospital

Day 1 (14 May 2015), 10:30-12:00

“BNCT as a new generation charged particle therapy - From Reactor to Accelerator –“

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Boron Neutron Capture Therapy (BNC) has been performed since several decades. Modernization of the BNCT has been developed in 1980's where boron compound borono-phenylalanine(BPA) become available as BNCT treatment agent as well as fluorinated BPA become available for PET scan in order to evaluate the BPA accumulation before BNCT.

Moreover, the treatment planning system for BNCT enabled precise 3 dimensional dosimetry for BNCT. Before having the treatment planning system, neutron flux were measured by sporadic points with gold wires.

Recently, the movement from nuclear reactor to accelerator is paradigm shift for BNCT and it enables the in-hospital treatment.

The review of the development of BNCT will be presented in the lecture.

Abstract for OIST mini symposium
“New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015
Title: “Introduction of accelerator-based neutron source for BNCT”
by: Prof. Hiroaki KUMADA, University of Tsukuba

Day 1 (14 May 2015), 10:30-12:00

Project of the development for an accelerator based BNCT in University of Tsukuba

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A project team (iBNCT project) headed University of Tsukuba is driving forward the development of an accelerator based neutron source for BNCT. The iBNCT project team consists of University of Tsukuba, High Energy Accelerator Research Organization (KEK), Japan Atomic Energy Agency (JAEA), Mitsubishi Heavy Industry Ltd. and Ibaraki prefecture. We are developing a high intensity linac based neutron source.

In iBNCT project, we have employed RFQ+DTL type linac as proton accelerator. Energy of the proton beam is specified to 8MeV. And we have selected beryllium as neutron target material. We were successful in accelerating protons to 8MeV using the linac in the end of 2014.

We have also constucted a neutron generator device consisting of Be target, moderator, collimator and radiation shield. To determine conceptual design of the device, Monte-Carlo analysis using the multi-purpose Monte-Carlo code; PHITS is being performed. The results of the Monte-Carlo analysis indicated that the neutron generator with 80kW proton beam can emit enough epithermal neutron flux as approximately 4.6×10^9 ($n/cm^2/s$) at the beam port.

In the project, we are developing not only the linac based neutron source but also medical equipment required in BNCT such as treatment planning system, patient setting device and radiation monitors.

Currently, we are carrying out the commissioning of the accelerator-based proton beam. We will complete the entire treatment device by the summer of 2015 and start generating neutrons using proton beam irradiation of the neutron generator. Subsequently, by gradually increasing the intensity of the proton beam, we will perform verification tests of the developed target system and evaluate the life and replacement frequency of the target, in addition to measuring the properties of the generated neutrons. Our plan is to generate neutrons with the intensity required for treatment in the year 2015, after which we intend to promptly begin clinical studies using this device.

Abstract for OIST mini symposium “New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015

Title: “Experiments of Ibaraki-BNCT accelerator commissioning”

By: Shin-ichi KUROKAWA, KEK / Cosylab

Day 1 (14 May 2015), 10:30-12:00

Present Status of Accelerator System and Its Challenges

Shin-ichi Kurokawa KEK and Cosylab

The accelerator system of iBNCT is an 8 MeV, high duty (20%) proton linac that supplies 80 kW beam down to the Be target for neutron production. These specs are quite challenging ones of this kind of linacs. This talk first introduces the present status of the accelerator system of iBNCT, and then discusses what kind of challenges we shall handle to achieve our goal.

Abstract for OIST mini symposium “New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015

Title:” Therapeutic strategies targeting cancer stem cells”

by: Prof. Hideyuki Saya, Keio University

Day 1 (14 May 2015), 13:00-14:00

Therapeutic strategies targeting cancer stem cells

Hideyuki Saya
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Cancer stem cells (CSCs) are a subset of tumor cells that are responsible for initiating and maintaining the disease. In the clinical point of view, the most important characteristics of CSCs include their resistance to chemotherapy and radiotherapy. However, the underlying mechanisms of the resistance remain unclear.

CD44 has been identified as a cell surface marker associated with cancer stem cells (CSCs) in several types of epithelial tumor. We have recently found that expression of CD44, in particular variant forms of CD44 (CD44v), contributes to the defense against reactive oxygen species (ROS) by promoting the synthesis of reduced gluathione (GSH), a primary intracellular antioxidant. CD44v interacts with and stabilizes xCT, a subunit of a glutamate-cystine transporter, and thereby promotes the uptake of cystine for GSH synthesis (***Cancer Cell*** 2011). Therefore, ablation of CD44 reduced GSH levels and increased ROS levels, leading to suppression of tumor growth and metastasis in both transgenic and xenograft tumor models (***Nat Commun*** 2012; ***Cancer Res*** 2013). Our findings reveal a novel function for CD44v in protection of CSCs from high levels of ROS generated by various treatments and tumor microenvironment. Based on these preclinical findings, we are currently conducting clinical trials using an xCT inhibitor for cancer patients having advanced gastric cancer and lung cancer.

Abstract for OIST mini symposium “New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015

Title: “Smart Targeted Therapy by Self-Assembled Supramolecular Nanosystems”

by: Prof. Kazunori Kataoka, the University of Tokyo

Day 1 (14 May 2015), 14:00-15:00

Smart Targeted Therapy by Self-Assembled Supramolecular Nanosystems

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Nanotechnology-based medicine (Nanomedicine) has received progressive interest for the treatment of intractable diseases, such as cancer, as well as for the non-invasive diagnosis through various imaging modalities. Engineered polymeric nanosystems with smart functions play a key role in nanomedicine, including drug carriers, gene vectors, and imaging probes. This presentation focuses present status and future trend of the development of self-assembled nanosystems from block copolymers for the therapy of intractable diseases.

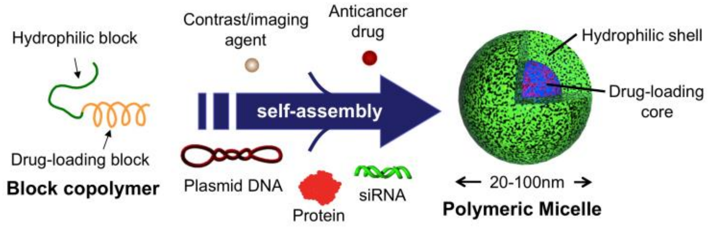

Fig. 1 Polymeric micelles as supramolecular nanomedicines

Nanosystems with 10 to 100 nm in size can be prepared by programmed self-assembly of block copolymers in aqueous entity. Most typical example is polymeric micelles with distinctive core-shell architecture (Fig. 1). Several micellar formulations of antitumor drugs have been intensively studied in preclinical and clinical trials, and their utility has been demonstrated[1,2]. Compared with conventional formulations, such as liposomes, polymeric micelles have several advantages, including controlled drug release, tissue penetrating ability and reduced toxicity. Critical features of the polymeric micelles as drug carriers, including particle size, stability, and loading capacity and release kinetics of drugs, can be modulated by the structures and physicochemical properties of the constituent block copolymers[3]. The development of smart polymeric micelles that dynamically change their properties due to sensitivity to chemical or physical stimuli is the most promising trend toward nanomedicines, directing to the targeting therapy with high efficacy and ensured safety. Notable anti-tumor efficacy against intractable cancer, including pancreatic cancer, of antitumor drug-incorporated polymeric micelles with pH-responding property was demonstrated to emphasize a promising utility of nanosystems for the cancer treatment[4-6].

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Abstract for OIST mini symposium “New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015

Title:” X-ray and Gamma-ray Telescopes used in Space and their Applications to Medical Imaging”

by: Prof. Tadayuki TAKAHASHI, Japan Aerospace Exploration Agency (JAXA)

Day 1 (14 May 2015), 15:30-17:00

Introduction to New Technology for X-ray and Gamma-ray Imaging

Tadayuki Takahashi
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The good energy resolution and the ability to fabricate compact arrays make semiconductor sensors very attractive for the imaging application in comparison with inorganic scintillation detectors coupled to either photodiodes or photomultiplier tubes. Though Si and Ge semi- conductors have been widely used, still, there are increasing demands for new semiconductor detectors capable of detecting hard X-ray and Gamma-rays. Cadmium telluride (CdTe) has been regarded as promising semiconductor materials for hard X-ray and gamma-ray detection, which can be operated at room temperature. Especially a large-area CdTe imaging detector with an area greater than a few tens of square centimeters with energy resolution of 1 to 2 keV (FWHM) is attractive for various applications.

The hard X-ray and gamma-ray bands have long been recognized as important windows for exploring the energetic universe. It is in these energy bands that non-thermal emission, primarily due to accelerated high-energy particles, becomes dominant. However, when compared with X-ray astronomy, hard X-ray and gamma-ray astronomy are still immature. In order to realize instruments providing much improved angular and spectral resolutions over the instruments in use today, we have been working on various types of CdTe detectors based on technologies such as electrodes on the device, ASICs for readout and hybridization for making large-scale detectors.

After 10 years of research and development, CdTe diode detectors have now entered the phase of actual application. In particular, the fine energy and position resolution obtained with CdTe pixel detectors or CdTe DSDs (Double Sided Detectors) are expected to lead to dramatically improved performance in the area of gamma-ray imaging. For astronomical observations, developments of Hard X-ray Imager (HXI) and Soft Gamma-ray Detector (SGD) based on the CdTe diode detectors are being progressed satisfactorily for the Japanese ASTRO-H satellite. HXI utilizes the large area CdTe DSD on the focal plane of the hard X-ray mirror while SGD is composed of 40-layer Si/CdTe Compton cameras. The direction of the gamma-ray is calculated by solving the Compton kinematics with information concerning deposit energies and interaction positions recorded in the detectors. A very compact, high-angular resolution (fineness of image) camera is realized by fabricating semiconductor imaging elements made of Si and CdTe, which have excellent performance in position resolution, high-energy resolution, and high-temporal resolution.

The technology developed here would also offer improved sensitivity in gamma-ray detection for various applications, including nuclear medical imaging, and nondestructive industrial imaging. In the field of medical imaging, a radiopharmaceutical, a pharmaceutical labeled by radioisotopes, injected into a living object need to be visualized. Although the potential performance of this kind of detector was proposed in early 1970s, adequate spatial resolution for medical use has not been achieved by traditional sensor technologies. It is only quite recently that semi-conductor based Compton Cameras has been made available. Since the CdTe imagers and the Si/CdTe semiconductor Compton camera have wide-band imaging capability from a few tens keV to MeV, various radioisotopes can be used. Moreover, simultaneous tracking of multiple radiopharmaceuticals could be realized by the capability to precisely distinguish emission lines from different radioisotopes.

Here we describe new technologies for X-ray and Gamma-ray imaging, which have been developed for highly sensitive detectors onboard high energy astronomy satellites. We also introduce our recent activities for future detectors, such as an electron-tracking Si/CdTe Compton camera.

Abstract for OIST mini symposium “New Medical Imaging and Advanced Cancer Therapy (BNCT) Instrumentation,” 14-16 May 2015
Title:” SOI Radiation Image Sensor for Medical Imaging and BNCT”
by: Prof. Yasuo ARAI, OIST

Day 1 (14 May 2015), 15:30-17:00

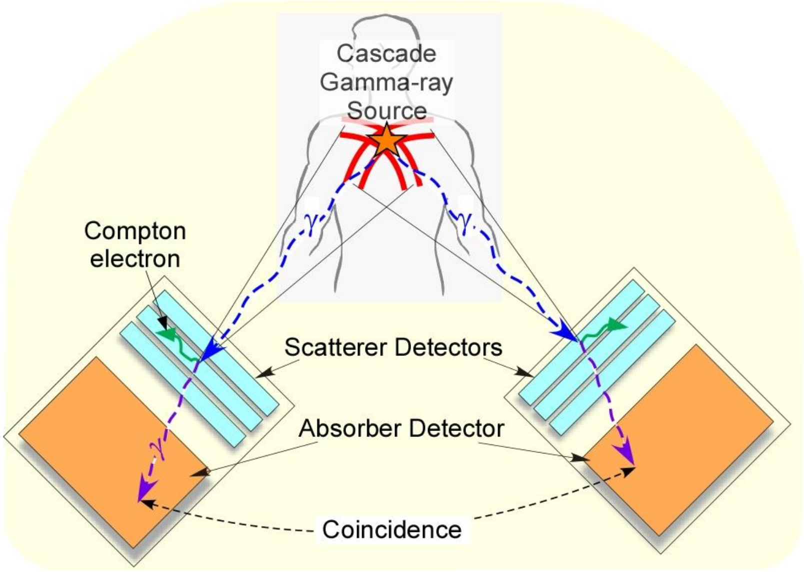
Monolithic Radiation Image Sensor with Silicon-On-Insulator

Yasuo Arai
Okinawa Institute of Science and Technology (OIST)
and
High Energy Accelerator Research Organization (KEK)

Radiation image sensors using a Silicon-On-Insulator (SOI) technology have been developed at KEK. By using the SOI technology, thick sensing region and CMOS readout circuit are implemented in a single die. Special process to realize such detector has been developed in collaboration with a semiconductor company.
The SOI pixel detector (SOIPIX) can achieve high resolution and good sensitivity due to its fine lithography of semiconductor process. In addition, it can be very intelligent by including in-pixel data processing circuit such as counter, comparator, memory, ADC, TDC, and so on.
The detector can be sensitive to many kinds of radiations (X-ray, electron, alpha, charged particles, neutron etc.), so various kinds of detectors are being developed through Multi Project Wafer (MPW) runs operated by KEK. Now this R&D is operated under Grant - in - Aid for Scientific Research (KAKENHI) on Innovative Areas, and has more than 50 collaborators.
Recent results and present status will be presented.

OIST Research Plan: Developing New Imaging Technologies

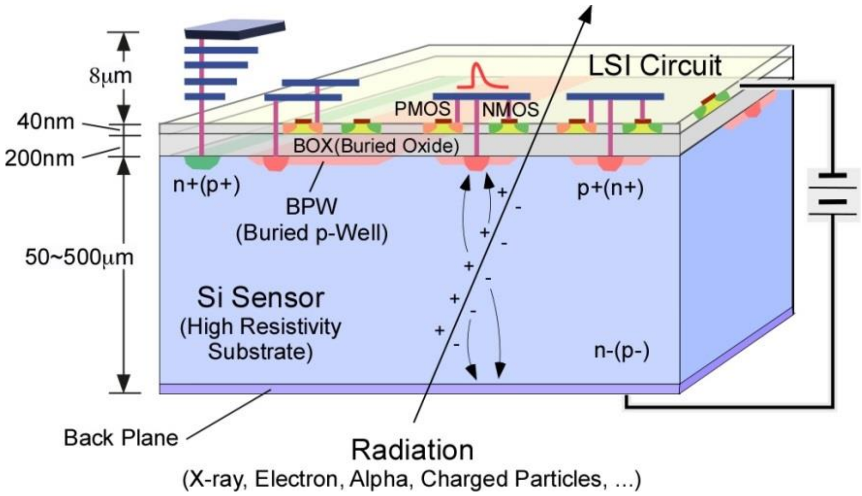
Imaging technology is one of the most emerging fields in recent years. Especially the field of medical imaging using many kinds of radiations such as X-ray, infrared light, charged particles, is a challenging area. Through this research, new radiation imaging devices using the latest semiconductor technologies will be developed with researchers at OIST.



Ultimately this research is expected to advance to the brain study actively done at OIST.

<u>Silicon-On-Insulator (SOI) technology</u>

Monolithic radiation image detector uses a SOI technology. Structure of a SOI pixel detector is shown below. In a SOI detector, each pixel can contain many transistors, thus data processing in each pixel can be possible. This enables new kind of measurement such as quantum counting, ultra-high speed image acquisition and so on.



Electron Tracking Compton Camera (ETCC)

An ETCC can determine the incident direction of the gamma-rays. This can be done by combining several layers of SOI pixel detectors and a segmented Ge detector (below). Determining the gamma-ray direction is very important not only in medical diagnoses such as SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography), but also in radiation therapy. The ETCC detector can also be used for surveying the radiation level in nuclear power plant or field. Furthermore it can be used to check deterioration of concrete of infrastructures such as bridge and tunnels by using back scattering X-ray.