# PRESENT STATUS OF CYCLOTRON FACILITY AT NIRS

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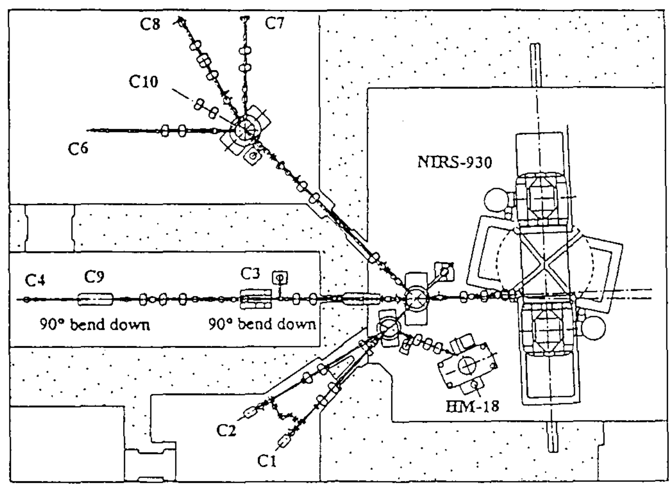
The NIRS-CHIBA isochronous cyclotron has been used for clinical trial of the eye melanoma, development of new radio-nuclides, radiation dosimetry, study of particle detectors and basic research of radiobiological experiments. An axial injection system was also equipped to provide intense heavy-ion beams for extension of the research fields. Since 1994, a new compact cyclotron has been utilized for PET. A brief review of the current status of the cyclotron operations and latest experiences in the field of applications are described.

## 1. INTRODUCTION

In 1975, the NIRS-Chiba isochronous cyclotron[1] (NIRS-930) was constructed for biomedical studies such as the clinical trials of fast neutron therapy, production of the short-lived radio-nuclides and preliminary study for proton therapy. The fast-neutron therapy, which had been the main purpose of the cyclotron and performed for almost twenty years, came to an end in December 1994, because a new facility of heavy ion accelerator complex HIMAC[2](Heavy Ion Medical Accelerator in Chiba) was started. The HIMAC has been operated routinely for clinical treatments of tumors since June 1994. In conjunction with the HIMAC operation a new small cyclotron(HM-18) was installed for PET, in 1994. The utilization of the NIRS-930, therefore, has been expanded into new research fields. The axial injection system was proposed[3] to provide various kinds of heavy-ions for these studies, and it was equipped with an external PIG type of ion source. The source tuning and the system operation are under testing.

The small cyclotron was set up just beside the NIRS-930 so as to good use of the existing R.I.-production ports. Fig.1 shows the present layout of the cyclotron facility. The target stations C1 and C2 are used for production of the short-lived radio-nuclides where the beams are provided from both cyclotrons, but not simultaneously. Weak magnetic interactions have been existing between two cyclotrons and their beam lines under the parallel operation. In order to minimize those effects we have managed to modify the beam optics on the NIRS-930 beam line together with fine adjustment of the outermost trimming coil.

Operation of those two cyclotrons is scheduled in the daytime from Monday afternoon to Friday except the regular maintenance time during two weeks of March and October annually.




C1, C2 : Production of R.I.s, C3 : Biological studies ( in preparation ),
C4 : Production of R.I.s for SPECT ( under planing ),
C6 : Studies of particle detectors, C7 : Radiobiological experiments,
C8 : Studies of radiation dosimetry, C9 : Proton therapy for eye,
C10 : Experiments of biophysics. ( under construction ).

Fig.1 Floor plan of NIRS cyclotron facility in June 1998.

## 2. OPERATIONS and IMPROVEMENTS

### 2-1. NIRS-930

The NIRS-930 cyclotron having K=110 consists of four sectors and two Dees (86 deg.) connected to moving panel type of rf-cavities. The frequency range of 11-21 MHz covers 1st and 2nd harmonic modes for the acceleration. The stable beams of proton with energy up to 70 MeV and heavy ions with energy up to 12MeV/u are sufficiently delivered with the extraction efficiencies of 50 ~ 70 %.

Various kinds of troubles along with the superannuation have occurred in the daily operation. The troubles are due mainly to the rf-control system and water cooling system, i.e., deterioration of the electronic parts and corrosion of distributing pipes of the water cooling system. In the rf-system, modules such as the low-level amplifiers and three phase detectors were replaced by new ones adopting latest electronic parts.

Table 1 shows the statistics of beam time distributions among the research fields in 1997.

Table 1. The distribution of beam time among research field.

| | | | | |
|---|---|---|---|---|
| 1. | Clinical trial of eye melanoma | 92.4 | h | ( 8.8 % ) |
| 2. | Production and development of: short-lived radio-nuclides | 212.5 | h | ( 20.2 % ) |
| 3. | Studies of particle detectors and radiation dosimetry | 525.9 | h | ( 49.9 % ) |
| 4. | Basic research of radiological experiments | 45.8 | h | ( 4.3 % ) |
| 5. | Maintenance and development | 176.5 | h | ( 16.8 % ) |
| | Total | 1053.1 | h | |

A poor development time was allowed during those several years due to care of the superannuation and installation of the small cyclotron. The development time was mostly used to adjust new beams with internal ion source and containing the axial injection system. At present, the overall transmission efficiencies of the axially injected beams were 10%, 8% and 6% with a rf-buncher for the q/m of 1/2,1/3 and 1/4 beams, respectively at the nearly maximum main fields.

A new beam stopper was equipped at the radius of 30cm in the cyclotron, which works in the interval of the beam delivery. As a result the residual radiation level was reduced by almost two order of magnitude around the deflector system.

In order to control the dose levels in the proton beam therapy, a quick beam shutter was equipped in the corresponding beam line. The beam stop time was faster than 150ms. The shutter is controlled by a medical specialist of the treatment side.

### 2-2. Small Cyclotron (HM-18)

Because of the clinical treatment of cancer therapy performed efficiently in the HIMAC, there is a great demand of diagnosis with PET. The HM-18 was designed specifically for production of short-lived radio-nuclides with $H^-$ (18 MeV) and $D^-$ (10 MeV) acceleration at the fixed rf-frequency of 45 MHz. Two thin graphite foils are located traveling in the opposite site, one for internal targets(having 4-assembled ports) and the other is for the external target station C1 and C2 (see in Fig1.). The beam transporting efficiencies from the cyclotron exit to the C1 and C2 have been achieved nearly 90% and 100 %, respectively.

Improvements were made on few points. A new beam stopper was also equipped inside the cyclotron where in the radius of 15cm to prevent the residual radioactivity in the cyclotron and to observe the beam loss on the acceleration.

Two oil diffusion pumps had been used as the main vacuum system, which were replaced by a turbo molecular pump(2000 l/s) and two cryopumps(8 and 10 inch), resulting in a better clean vacuum due to lack of oil back.

## 3. APPLICATIONS

### 3-1. Proton therapy of the eye

Range of the 70 MeV proton beam is about 4 cm in water. This beam is suitable for the therapy of the eye, because tumors of the eye seat about 2-3 cm in depth. There are many proton facilities for the eye treatment, because the results of the eye treatment are satisfactorily good. In our cyclotron facility, we also developed irradiation port for the eye treatment using a vertical course of the 70 MeV proton beam. By using the vertical course, patient immobilitation devices are very simple and patients can be very relax to take the treatments. In Japan, the incidence of the eye melanoma is very small, about 10 patients per year in whole of Japan. However, it is sometimes required to treat very large tumors.

In order to treat such large tumor, we have developed a proton treatment system using bolus to define the shape of the distal part of the irradiation target. Using this bolus technique, it has been possible to avoid the irradiation of optic nervous near the eye ball.

### 3-2. Radiobiological Effects of Mixed Ion Beams[4]

HIMAC the new facility for cancer radiotherapy, was founded at the NIRS. The use of heavy-ion beams for cancer therapy requires the moderation of a primarily narrow Bragg peak into one that is broad. It will usually cause a continuous fluctuation of the linear energy transfer (LET) values throughout the spread-out Bragg peak (SOBP). The fluctuation of the LET causes a fluctuation of the biological effectiveness. This phenomenon must be taken into account in designing the SOBP. Biological responses of cells exposed to ionization radiations are ordinary discussed in terms of survival curves with its parameters. The response shows maximum at around 100-200 keV/$\mu$m as its LET, and the shape of survival curve changes with LET. In the designing the SOBP beam, we assumed that the survival curves and its parameters may be dose averaged values of each primary monoenergetic beams. The study has been made to verify the hypothesis with biological experiments. The survival curves for mixed and monoenergetic beams were determined, and compared with the theoretical calculations. Chinese hamster V79 cells were exposed to low LET(high energy, 135 or 290 MeV/u) carbon beams that obtained from HIMAC and high LET (low energy, 12 MeV/u) carbon beams that obtained from the NIRS-930. In the experiments, we chosen several sets of too different monoenergetic beams, where the LET was adjusted by inserting adequate absorber between beam exit and sample. The experimental results and the calculation showed good agreement.

### 3-3. Production of Short-lived Radiopharmaceuticals

Since 1974, short-lived isotopes such as $^{11}C$, $^{13}N$, $^{15}O$, $^{18}F$, $^{38}K$, $^{52}Fe$, $^{62}Zn$, $^{77}Br$, $^{77}Kr$ and $^{123}I$ have been produced, labeled to biologically interesting compounds and used for clinical and animal studies at NIRS. In the recent ten years, positron emitters, $^{11}C$ (half life $T_{1/2}$ = 20 min.), $^{13}N$ ($T_{1/2}$ = 10 min.), $^{15}O$ ($T_{1/2}$ = 2 min.), $^{18}F$ ($T_{1/2}$ = 110 min.) and $^{38}K$ ($T_{1/2}$ = 7.6 min.) have been mainly produced for the studies of brain function, cancer imaging, myocardial blood flow measurement and so on, in conjunction with positron emission tomography (PET). [$^{11}C$]methionine and [$^{18}F$]FDG have been routinely produced before and after the treatment by heavy ions to cancer patients, to evaluate the effectiveness of the cancer therapy by heavy ions from HIMAC. Many $^{11}C$-labeled radiopharmaceuticals, [$^{11}C$]FLB457, [$^{11}C$]SCH23390, [$^{11}C$]N-methylspiperone, [$^{11}C$](+)McN5652-X, [$^{11}C$]NMPB, [$^{11}C$]Ro15-1788, etc. have been produced and used for the diagnosis of psychoneurosis, i.e., schizophrenia, depression, Alzheimer's disease, etc. [$^{13}N$]$NH_3$ and [$^{38}K$]$K^+$ have been used for the evaluation of a myocardial and renal blood flow. Table 2 shows the radiopharmaceuticals produced in 1997.

At NIRS, a great effort has been made to develop quick and automated production system for short-lived radiopharmaceuticals and to achieve high specific activity. Until now, several automated equipment have been developed for the production of $^{11}C$-labeled compounds with [$^{11}C$]$CH_3I$ as a precursor[5], [$^{38}K$]$K^+$ [6] and $^{13}N$-labeled compounds with anhydrous [$^{13}N$]$NH_3$[7] and so on, which enable the production of the corresponding compounds with enough radioactivity and radiochemical purity to carry out PET study within ~ one half-life. Theoretical value of specific activity for short-lived isotopes is quite high, e.g. 3.4 x $10^5$ GBq/$\mu$mol for $^{11}C$. However, practically attainable value is not so high due to the isotopic dilution from circumstances, e.g., 10 ~ 100 GBq/$\mu$mol for $^{11}C$-labeled compounds. We could achieve more than 400 GBq/$\mu$mol for $^{11}C$-, $^{13}N$-, $^{18}F$- and $^{38}K$-labeled compounds by cleaning production system, shortening the synthesis time, purifying reagents and so on.

Recently, we have developed a new production system for $^{38}K^+$, equipped with a heating and a cooling device on a target chamber for quick recovery. 20 bars of a natural argon gas was loaded into the target chamber (150 mm length) and irradiated by 40 MeV ( 39.2 MeV on target ) protons from the NIRS-930 at 6 ~ 6.5 $\mu$A for 15 min. By the $^{nat}Ar(p,3n)^{38}K$ reaction, 610 ± 30 MBq of $^{38}K^+$ could be obtained within 2.2 ± 0.4 min. at radiochemical purity >99.9 % and specific activity 690 ± 140 GBq/$\mu$ mol.

At NIRS, a new facility is now under construction, which enables fully automated production of short-lived radiopharmaceuticals including quality control, dispensation and documentation.

### 3-4. Dosimetry with different walled ionization chambers

The absorbed dose to water for proton beams were determined using several Farmer type ionization chambers with different wall and build-up cap materials. We prepared five different wall and build-up cap combinations as PMMA -PMMA, Nylon-PMMA, Carbon-Delrin, A-150-Lucentine and C-552-Polystyrene, respectively. All ionization chambers are same geometrical condition without very small difference of length and diameter of outer and central electrode. Absorbed dose measurements were carried out for 70 MeV proton beam. Irradiations were made at the entrance plateau for mono-energetic beam. Irradiations were carried out in air without build-up cap. One of the most important problem in the experiment of dose comparison is the stability of beam monitor. In order to check the stability of the beam monitor, measurements were repeated regularly using a reference ionization chamber. Then, the stability was estimated within 0.2% for the proton beam. For all chamber irradiations, measurements were made for both positive and negative polarities. Polarity effect for all chambers was less than 0.05% for the proton beam. Actually, absorbed dose was calculated using the average value for both polarities. The ionization chamber readings were converted to absorbed dose to water according to the JARP (Japanese Association of Radiological Physicists) protocol. The dose was explained in Gy for appropriate monitor counts. Any corrections were made for the very small differences among the ionization chamber geometry. The range of variation of the absorbed dose estimated for all chambers was within ± 0.5% for the proton beam. We can conclude that the absorbed dose to water for heavy ion beams, which was determined with several Farmer type ionization chambers,

Table 2. Production of Radio-isotopes in 1997 at NIRS

| Nuclide | Compound | GBq | n1 | n2 | n3 | comments |
|---|---|---|---|---|---|---|
| 11C | SCH23390 | 46.3 | 16 | 0 | 0 | brain study |
| | N-Methylspiperone | 72.9 | 22 | 12 | 0 | brain study |
| | cyanoimipramine | 1.7 | 1 | 0 | 1 | brain study |
| | CH3I | 20.3 | 9 | 0 | 0 | synthesis |
| | NMPB | 71.7 | 29 | 18 | 2 | brain study |
| | alanine | 122.9 | 52 | 0 | 0 | synthesis |
| | L-methyonine | 750.6 | 174 | 164 | 1 | cancer study |
| | Ro15-4513 | 4.2 | 1 | 0 | 0 | brain study |
| | MP4A | 101.5 | 38 | 37 | 0 | brain study |
| | (+)McN5652 | 25.9 | 14 | 12 | 0 | brain study |
| | (-)McN5652 | 26.3 | 15 | 15 | 0 | brain study |
| | FLB457 | 71.4 | 57 | 39 | 0 | brain study |
| | others | 54.9 | 55 | 0 | 0 | synthesis |
| 13N | NH3 | 29.6 | 35 | 0 | 13 | blood flow |
| | others | 11.7 | 8 | 0 | 2 | synthesis |
| 15O | H2O | 216.1 | 169 | 150 | 0 | blood flow |
| 18F | FDG | 115.2 | 53 | 48 | 4 | cancer & brain |
| | others | 20.2 | 29 | 0 | 5 | synthesis |
| 38K | K+ | 14.4 | 34 | 0 | 16 | blood flow |

n1: number of productions
n2: number of delivery for clinical applications
n3: number of delivery for animal experiments

shows good agreement within ±0.5% according to the protocol. The small difference of the absorbed doses may be depend on inaccuracy of physical constants used for the chamber calibration.

### 3-5. Low LET particle detection with CR-39

Recently Atomic Force Microscopy (AFM) has been applied to image for the track etch pits and the surface of CR-39[8,9]. In this technique, the CR-39 is etched for a very short time. Etch pits of several hundred nano meters can be observed. We applied this technique to CR-39 detection for the low LET (liner energy transfer) particle. CR-39 has found wide application to various fields such as heavy ion nuclear physics, cosmic ray physics and radiation dosimetry because of its simplicity in handling and availability at a low price. These investigations is advanced using the fact that a charged particle produces a latent track on the CR-39 as a result of damage caused by the energy deposition of the particle. For the irradiation of the low LET particle, it is difficult to distinguish the etch pits with the roughness of the surface by the etching. Using the optical microscope (OPT) observation technique, the tracks of protons up to the energy of 16 MeV can be measured. The copolymer of CR-39 monomer with N-isopropylacrylamide(NIPPAm) which developped by Ogura et al.[10] can be record tracks of protons up to the energy of 27 MeV. If the AFM method can be detected particles of lower LET than this technique possible, the application range of this detector will extend in the various field. The AFM observation has been applied to evaluate the surface roughness and the track sensitivity for CR-39 detectors. The experiments have been done for three types of detector (pure CR-39, CR-39 doped with antioxidant and copolymer of CR-39/NIPAAm) varying with the etching time up to 24 hours in 7N-NaOH at 70℃. As a result, the general circumstances of the progressing of locally non-uniform etching were clearly observed with increasing in the etching time. The CR-39 were also exposed to beam of 20, 25 and 30 MeV protons. Using the OPT and AFM methods, we are now progress in the etch pit analysis.

### 3-6. Performance of a Phoswich Neutron Detector for Space Application.

In the space environment, many secondaries are produced through interactions of cosmic ray primaries with spacecraft walls. The contribution of neutrons to the radiation exposure of astronauts must be studied due to its poor information. We have developed a new phoswich neutron detector consisting of an NE213 liquid scintillator surrounded by an NE115 plastic scintillator to measure high energy neutron spectra accurately in space. Differences in the decay time constants of light outputs from the two scintillators make it possible to separate charged-particle-induced and neutron-induced pulses. We produced mixed fileds of neutrons and protons by bombarding 70MeV protons on a 2mm thick Be target. Protons elastically scattered by the Be target and neutrons produced by the Be(p,xn) reactions were detected with the detector. A two-dimensional spectrum of the light outputs measured with the detector is presented in Fig.2. The component "A", the four components "B" through "E", and the two components "F" and "G" are due to gamma rays, neutrons and external protons, respectively. This phoswich detector was found to be able to clearly discriminate neutron and gamma-rays events from external proton events at about 60MeV energy.

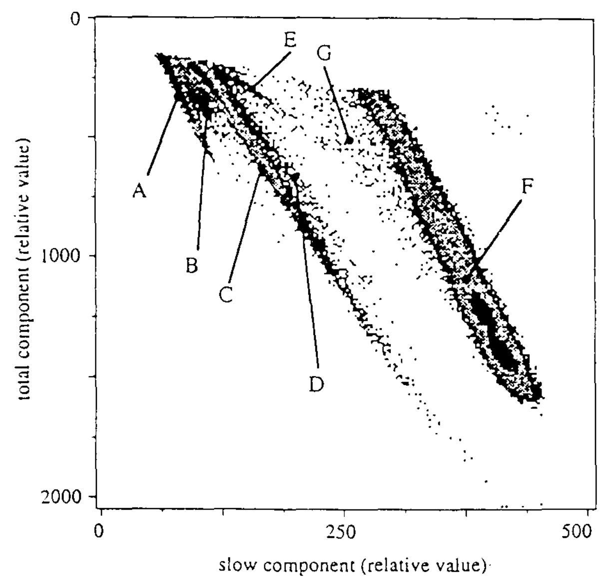



Fig.2. Two dimensional spectrum of Be (p,xn) reactions.

## ACKNOWLEDGMENTS

The authors wish to thank the technical staffs; K.Nemoto, Y.Kuramochi, R.Ohta, S.Hojo and K.Miyamoto of the NIRS cyclotron facility for their helpful operation and maintenance. We would like to thank Dr. Y.Hirao for his continuous encouragement.

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