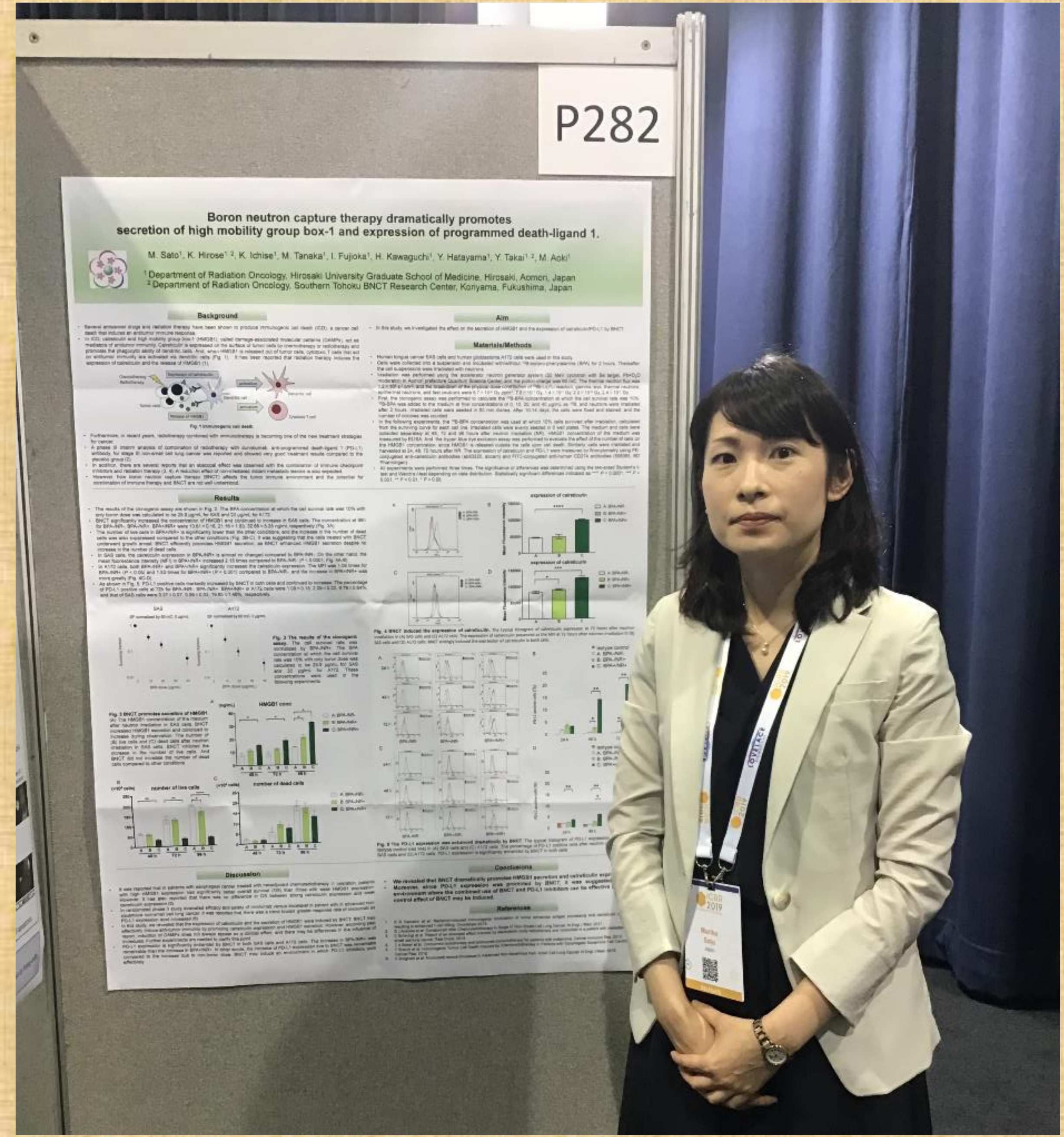
ICRR 2019

2019/08/25-29



Boron neutron capture therapy dramatically promotes secretion of high mobility group box-1 and expression of programmed death-ligand 1.

M. Sato[1], K. Hirose[1, 2], K. Ichise[1], M. Tanaka[1], I. Fujioka[1], H. Kawaguchi[1], Y. Hatayama[1], Y. Takai[1, 2], M. Aoki[1]

[1] Department of Radiation Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan
[2] Department of Radiation Oncology, Southern Tohoku BNCT Research Center, Koriyama, Fukushima, Japan

Background

Aim

Materials/Methods

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Conclusions

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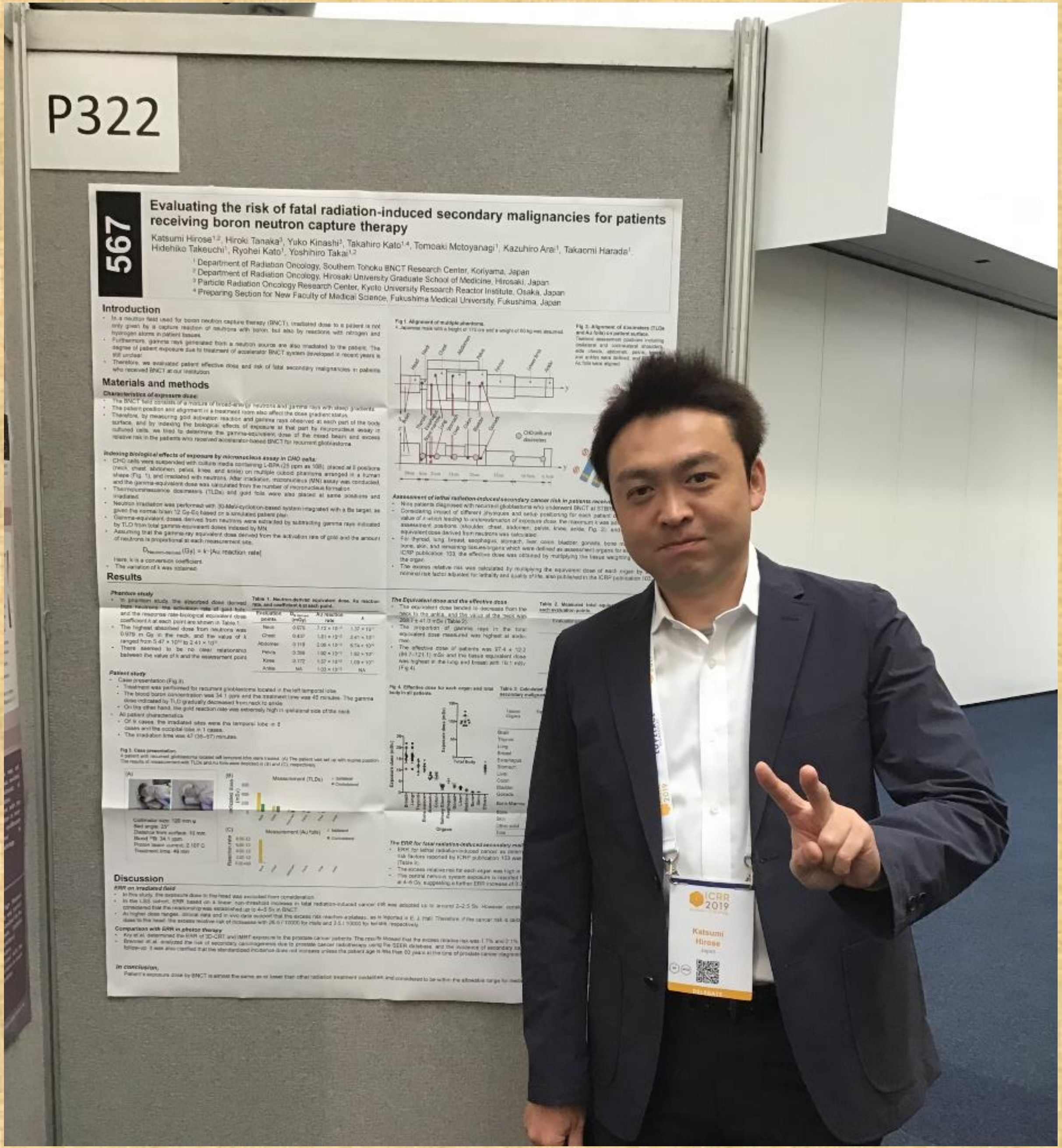

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Evaluating the risk of fatal radiation-induced secondary malignancies for patients receiving boron neutron capture therapy

Katsumi Hirose[1,2], Hiroki Tanaka[3], Yuko Kinashi[3], Takahiro Kato[1,4], Tomoaki Motoyanagi[1], Kazuhiro Arai[1], Takaomi Harada[1], Hidehiko Takeuchi[1], Ryohei Kato[1], Yoshihiro Takai[1,2]

[1] Department of Radiation Oncology, Southern Tohoku BNCT Research Center, Koriyama, Japan
[2] Department of Radiation Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
[3] Particle Radiation Oncology Research Center, Kyoto University Research Reactor Institute, Osaka, Japan
[4] Preparing Section for New Faculty of Medical Science, Fukushima Medical University, Fukushima, Japan

Introduction

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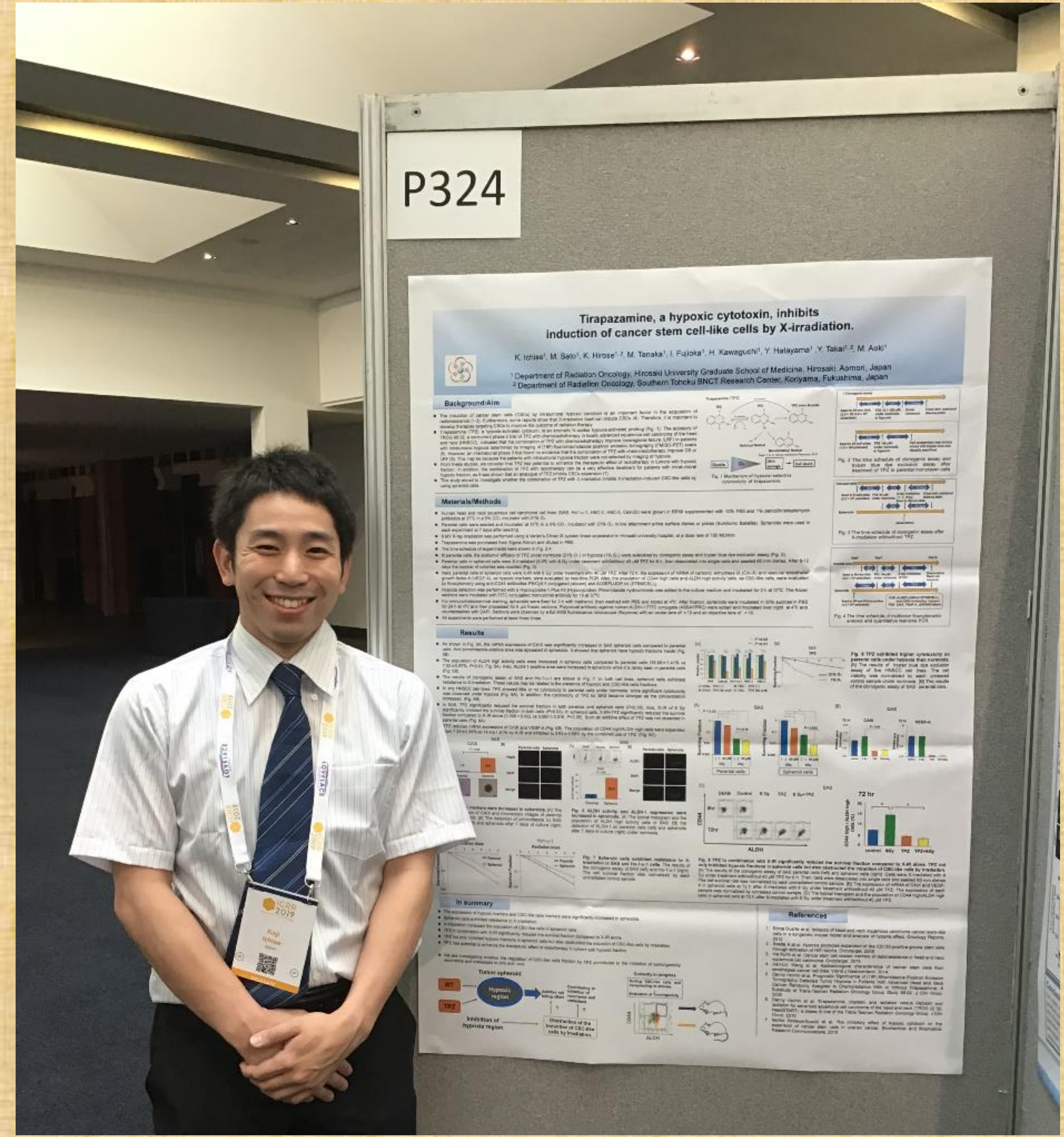

P324

Tirapazamine, a hypoxic cytotoxin, inhibits induction of cancer stem cell-like cells by X-irradiation.

K. Ichise[1], M. Sato[1], K. Hirose[1, 2], M. Tanaka[1], I. Fujioka[1], H. Kawaguchi[1], Y. Hatayama[1], Y. Takai[1, 2], M. Aoki[1]

[1] Department of Radiation Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan
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Background/Aim

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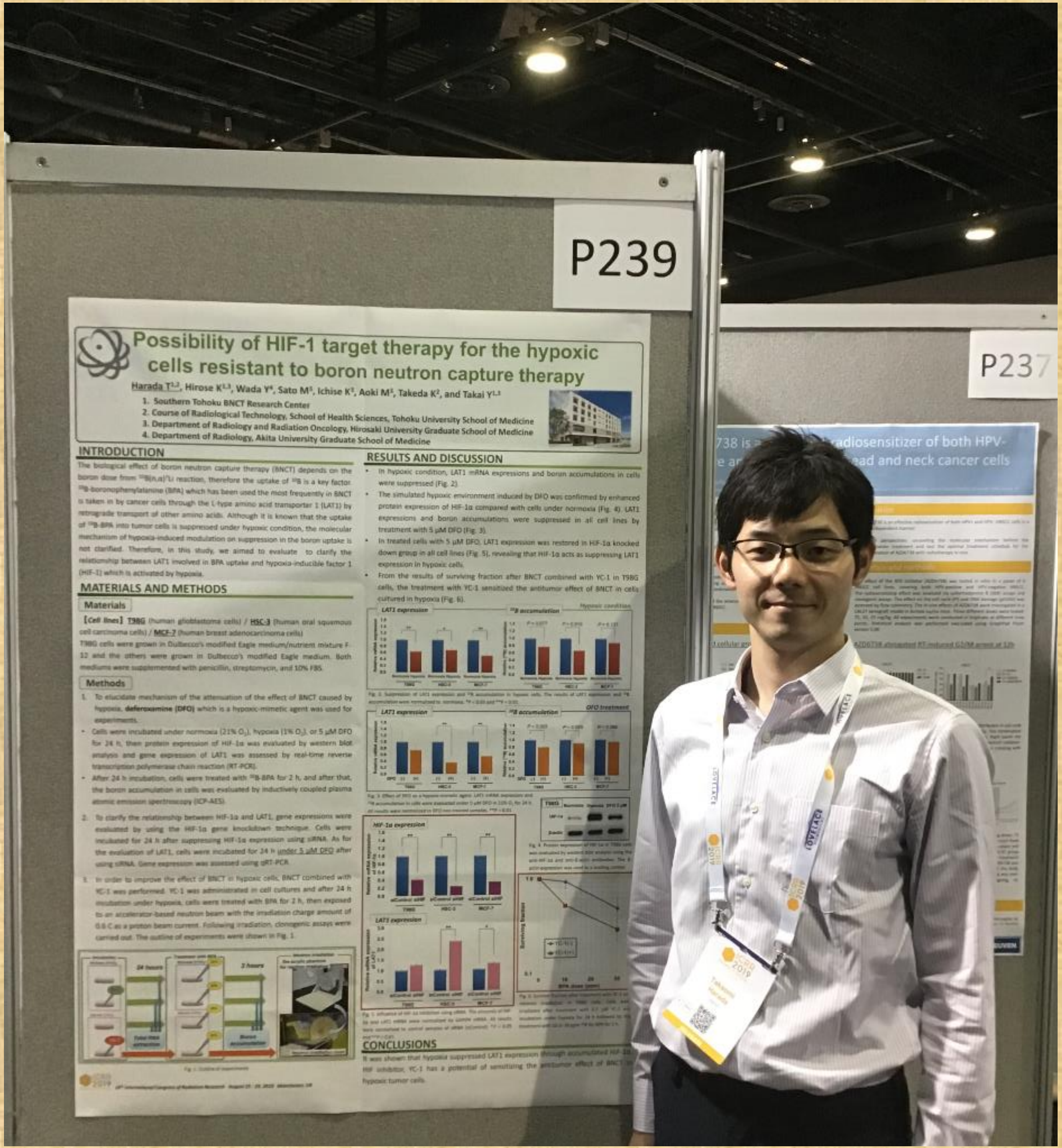

P239

Possibility of HIF-1 target therapy for the hypoxic cells resistant to boron neutron capture therapy

Harada T[1,2], Hirose K[1,3], Wada Y[4], Sato M[3], Ichise K[3], Aoki M[3], Takeda K[2], and Takai Y[1,3]

1. Southern Tohoku BNCT Research Center
2. Course of Radiological Technology, School of Health Sciences, Tohoku University School of Medicine
3. Department of Radiology and Radiation Oncology, Hirosaki University Graduate School of Medicine
4. Department of Radiology, Akita University Graduate School of Medicine

INTRODUCTION

The biological effect of boron neutron capture therapy (BNCT) depends on the boron dose from $^{10}B(n,\alpha)^{7}Li$ reaction, therefore the uptake of ^{10}B is a key factor. ^{10}B-boronophenylalanine (BPA) which has been used the most frequently in BNCT is taken in by cancer cells through the L-type amino acid transporter 1 (LAT1) by retrograde transport of other amino acids. Although it is known that the uptake of ^{10}B-BPA into tumor cells is suppressed under hypoxic condition, the molecular mechanism of hypoxia-induced modulation on suppression in the boron uptake is not clarified. Therefore, in this study, we aimed to evaluate to clarify the relationship between LAT1 involved in BPA uptake and hypoxia-inducible factor 1 (HIF-1) which is activated by hypoxia.

MATERIALS AND METHODS

Materials

【Cell lines】 T98G (human glioblastoma cells) / HSC-3 (human oral squamous cell carcinoma cells) / MCF-7 (human breast adenocarcinoma cells)

T98G cells were grown in Dulbecco's modified Eagle medium/nutrient mixture F-12 and the others were grown in Dulbecco's modified Eagle medium. Both mediums were supplemented with penicillin, streptomycin, and 10% FBS.

Methods

1. To elucidate mechanism of the attenuation of the effect of BNCT caused by hypoxia, **deferoxamine (DFO)** which is a hypoxic-mimetic agent was used for experiments.
   - Cells were incubated under normoxia (21% O_2), hypoxia (1% O_2), or 5 μM DFO for 24 h, then protein expression of HIF-1α was evaluated by western blot analysis and gene expression of LAT1 was assessed by real-time reverse transcription polymerase chain reaction (RT-PCR).
   - After 24 h incubation, cells were treated with ^{10}B-BPA for 2 h, and after that, the boron accumulation in cells was evaluated by inductively coupled plasma atomic emission spectroscopy (ICP-AES).
2. To clarify the relationship between HIF-1α and LAT1, gene expressions were evaluated by using the HIF-1α gene knockdown technique. Cells were incubated for 24 h after suppressing HIF-1α expression using siRNA. As for the evaluation of LAT1, cells were incubated for 24 h under 5 μM DFO after using siRNA. Gene expression was assessed using qRT-PCR.
3. In order to improve the effect of BNCT in hypoxic cells, BNCT combined with YC-1 was performed. YC-1 was administrated in cell cultures and after 24 h incubation under hypoxia, cells were treated with BPA for 2 h, then exposed to an accelerator-based neutron beam with the irradiation charge amount of 0.6 C as a proton beam current. Following irradiation, clonogenic assays were carried out. The outline of experiments were shown in Fig. 1.

RESULTS AND DISCUSSION

- In hypoxic condition, LAT1 mRNA expressions and boron accumulations in cells were suppressed (Fig. 2).
- The simulated hypoxic environment induced by DFO was confirmed by enhanced protein expression of HIF-1α compared with cells under normoxia (Fig. 4). LAT1 expressions and boron accumulations were suppressed in all cell lines by treatment with 5 μM DFO (Fig. 3).
- In treated cells with 5 μM DFO, LAT1 expression was restored in HIF-1α knocked down group in all cell lines (Fig. 5), revealing that HIF-1α acts as suppressing LAT1 expression in hypoxic cells.
- From the results of surviving fraction after BNCT combined with YC-1 in T98G cells, the treatment with YC-1 sensitized the antitumor effect of BNCT in cells cultured in hypoxia (Fig. 6).

CONCLUSIONS

It was shown that hypoxia suppressed LAT1 expression through accumulated HIF-1α. HIF inhibitor, YC-1 has a potential of sensitizing the antitumor effect of BNCT in hypoxic tumor cells.


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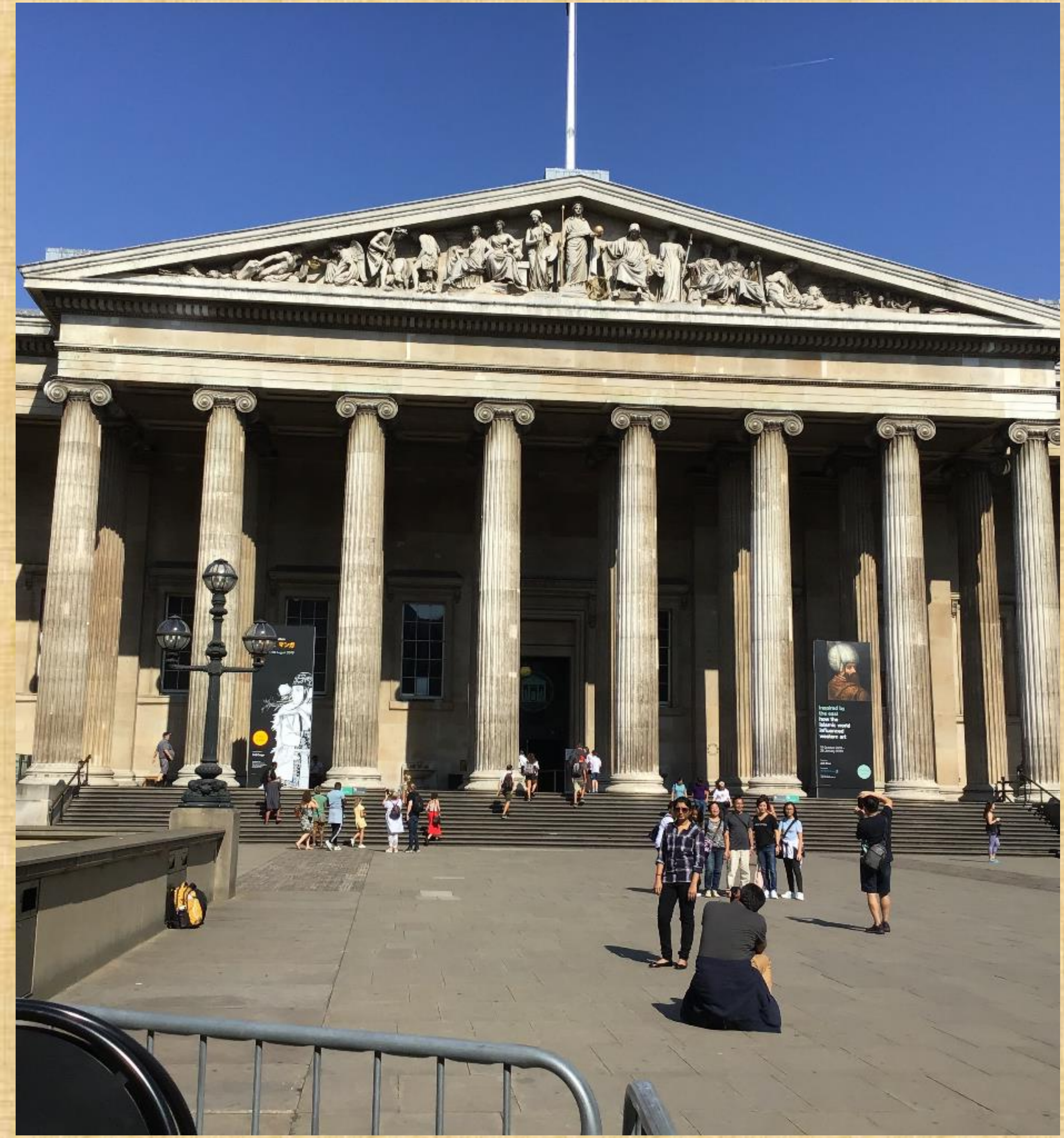
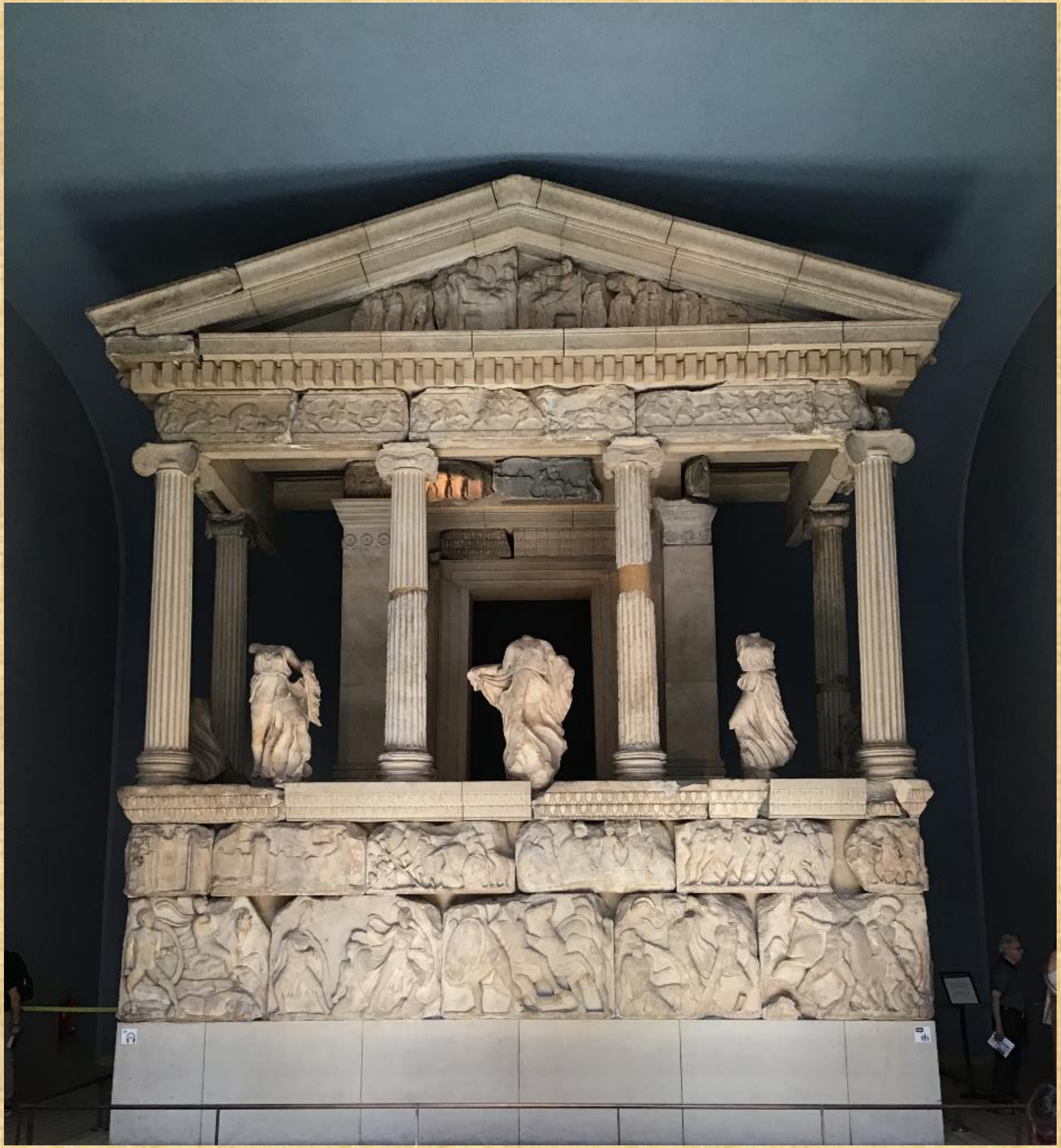
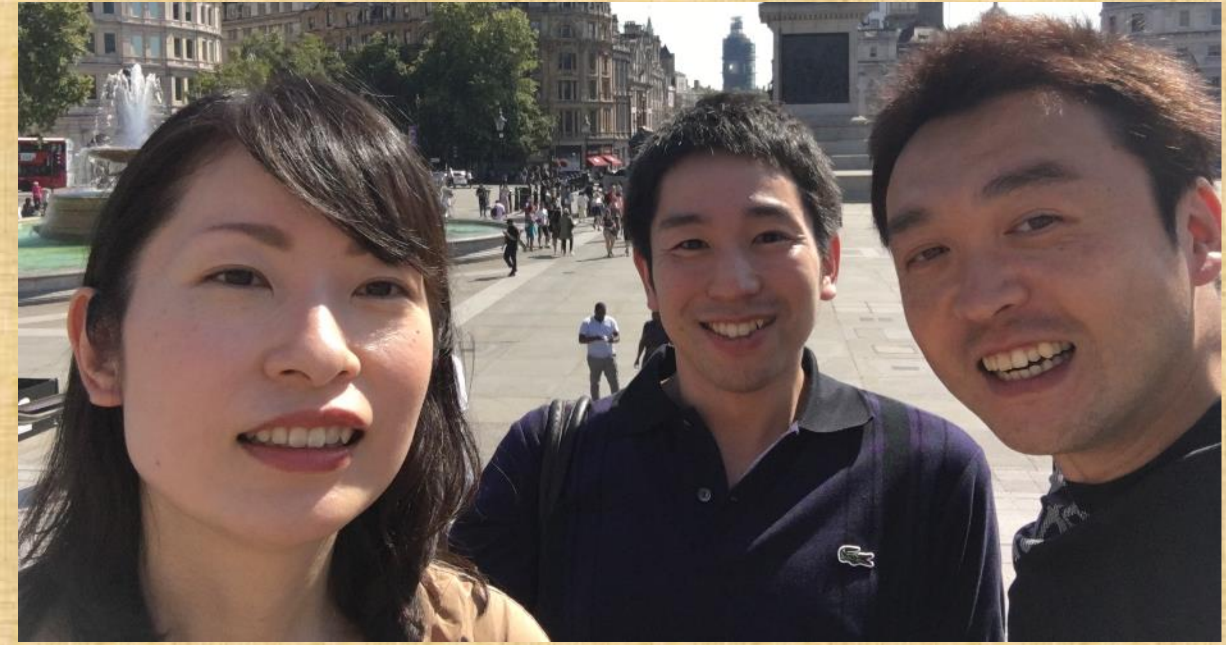
Entrance this way
PEDESTRIAN ZONE


Inspired by the east
how the Islamic world influenced western art



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