International Joint Symposium 2020

The 15th International Workshop on Biomaterials in Interface Science

The 11th Symposium on Innovative Dental-Engineering Alliance (IDEA)

Program and Abstracts

Online meeting

December 14–15, 2020

Schedule at a Glance

14 Dec. 2020

Start	Time	No.		Speaker
Opening Session				
9:00	0:05		Opening address	Nobuhiro TAKAHASHI
Session I: Oral Health Care				Chair: Hiroshi EGUSA
9:05	0:30	I-01	Invited Lecture	Sei Kwang Hahn
9:35	0:20	O-01	Oral talk	Kyosuke Ueda
9:55	0:20	O-02	Oral talk	Haruki Otani
10:15	0:20	O-03	Oral talk	Fumitoshi Ohori
10:35	0:15	Break		
Session II: IDEA				Chair: Hideki HOSODA
10:50	0:30	I-02	Invited Lecture	Frédérique Vanholsbeeck
11:20	0:20	O-04	Oral talk	Shoichi Hasegawa
11:40	0:20	O-05	Oral talk	Ryo Hamai
12:00	0:20	O-06	Oral talk	Takashi Obi
12:20	1:00	Break		
Session III: Biomaterials				Chair: Osamu SUZUKI & Masakazu KAWASHITA
13:20	0:30	I-03	Invited Lecture	Masato Ueda
13:50	0:20	O-07	Oral talk	Peng Chen
14:10	0:20	O-08	Oral talk	Jiang Jing
14:30	0:20	O-09	Oral talk	Weidong Zhang
14:50	0:20	O-10	Oral talk	Yingchen Wang
15:10	0:15	Break		
Session IV: Industry-academia-government collaboration				Chair: Keiichi SASAKI
15:25	0:30	I-04	Invited Lecture	Shipei Sato
15:55	0:20	O-11	Oral talk	Weiwei Zhou
16:15	0:20	O-12	Oral talk	Shokouh Attarilar
16:35	0:20	O-13	Oral talk	Nobuyuki Morimoto

15 Dec. 2020

Start	Time	No.		Speaker
Session V: Young innovators'session				Chair: Jumpei WASHIO & Wan-Ting CHIU
9:00	0:30	I-05	Invited Lecture	Guangyin Yuan
9:30	0:20	O-14	Oral talk	Naohiro Sugita
9:50	0:20	O-15	Oral talk	Wan–Ting Chiu
10:10	0:20	O-16	Oral talk	Hiroki Chigama
10:30	0:15	Break		
Session VI: Bioengineering				Chair: Ryoichi NAGATOMI
10:45	0:30	I-06	Invited Lecture	Ming-Long Yeh
11:15	0:20	O-17	Oral talk	Ryo Shintate
11:35	0:20	O-18	Oral talk	Daixiu Wei
11:55	0:20	O-19	Oral talk	Ariunbuyan Sukhbaatar
Closing Session				
12:15	0:05		Closing	Takao HANAWA

Technical Program

Monday, December 14

Opening Session (9:00–9:05)

Opening address

Nobuhiro TAKAHASHI, Tohoku University, Japan

Session I
Oral Health Care (9:05–10:35)

Chair: Hiroshi EGUSA, Tohoku University, Japan

I-01 (invited)

"Multifunctional Biomaterials for Smart Wearable Healthcare Devices"

Sei Kwang Hahn

Pohang University of Science and Technology, Korea

O-01

"Effect of Ta Addition on the Antibacterial Activity and Cytotoxicity of Ag containing Amorphous Calcium Phosphate Coating Film"

Kyosuke Ueda

Tohoku University, Japan

O-02

"Periodontitis-associated bacterial culture supernatants inhibit the glucose metabolic activity of host cells"

Haruki Otani

Tohoku University, Japan

O-03

"TNF-α Directly and Indirectly Induces RANKL Expression on Osteocytes during Orthodontic Tooth Movement"

Fumitoshi Ohori"

Tohoku University, Japan

Break (10:35–10:50)

Session II
IDEA (10:50–12:20)

Chair: Hideki HOSODA, Tokyo Institute of technology

I-02 (invited)

"Birefringence as a proxy for viscoelastic properties of cartilage using polarisation sensitive optical coherence tomography"

Frédérique Vanholsbeeck

The Dodd-Walls Centre for Photonic and Quantum Technologies, New Zealand

O-04

"Haptic interaction with deformable objects and various materials based on physics simulations"

Shoichi Hasegawa

Tokyo Institute of Technology, Japan

O-05

"**Comparative study of capacity of protein adsorption onto octacalcium phosphate prepared by different synthesis conditions**"

Ryo Hamai,

Tohoku University, Japan

O-06

"**Binary Malignancy Classification of Skin Tissue using Reflectance and Texture Features from Macropathology Multi-Spectral Images**"

Takashi Obi

Tokyo Institute of Technology, Japan

Break (12:20–13:20)

Session III
Biomaterials (13:20–15:10)

Chair: Osamu SUZUKI, Tohoku University, Japan
Masakazu KAWASHITA, Tohoku University, Japan

I-03 (invited)

"**Utilisation of Ceramic films in Biomedical and Environmental Applications**"

Masato Ueda
Kansai University, Japan

O-07

"**Improvement of osteoconduction of preosteoblast by titanium with patterned periodic nano surface topography fabricated by femtosecond laser irradiation**"

Peng Chen
Tokyo Medical and Dental University, Japan

O-08

"**The effect of cryogenic thermal cyclic processing on the mechanical properties of TiNi based crystalline/amorphous alloy**"

Jiang Jing
Tohoku University, Japan

O-09

"**Physical properties of Ti-36Nb-2.0Ta-3.0Zr-0.35O alloy prepared by powder metallurgy**"

Weidong Zhang
Hunan University, China

O-10

"**Microstructure evolution and deformation behavior of graphene oxide induced TiC reinforced Ti6Al4V processed by friction stir processing**"

Yingchen Wang
Shanghai Jiao Tong University, China

Break (15:10–15:25)

Session Ⅳ
Industry-academia-government collaboration (15:25–16:50)

Chair: Keiichi SASAKI, Tohoku University, Japan

I-04 (invited)

"**Entrepreneurship from University Seeds and Second Foundation**"

Shinpei Sato

Acuity inc, Japan

O-11

"**Effectof oxygen content onthemelting behavior of stainless-steelpowdersfor laser additive manufacturing**"

Weiwei Zhou

Tohoku University, Japan

O-12

"**Nanomodification of dental implants to improve its mechanical and biological performance"**

Shokouh Attarilar

Shanghai Jiao Tong University, China

O-13

"**Sulfobetaine polymer conjugates for anticancer drug delivery to cell spheroids**"

Nobuyuki Morimoto

Tokyo Institute of Technology, Japan

Tuesday, December 15

Session Ⅴ
Young innovators' session (9:00–10:30)

Chair: Jumpei WASHIO, Tohoku University, Japan
Wan-Ting CHIU, Tokyo Institute of Technology, Japan

I-05 (invited)

"**Viewpoints on R&D of innovative biodegradable Mg alloys from the aspect of accelerating clinical transformation**"

Guangyin Yuan

Shanghai Jiao Tong University, China

O-14

"**Nonlinear resonance of a ball-impact electromagnetic energy harvester for low frequency vibration**"

Naohiro Sugita

Tokyo Institute of Technology, Japan

O-15

"**Developments of Flexible and Biocompatible Hybrid Materials towards the Glucose Sensing Applications**"

Wan Ting Chiu

Tokyo Institute of Technology, Japan

O-16

"**Antibacterial activity of calcium-doped raw silk fabric**"

Hiroki Chigama

Tohoku University, Japan

Break (10:30–10:45)

Session Ⅵ
Bioengineering (10:45–12:15)

Chair: Ryoichi NAGATOMI, Tohoku University, Japan

I-06 (invited)

"**Gallic-acids Loaded PLGA Coating on Biodegradable ZK60**"

Ming-Long Yeh

National Cheng Kung University, Taiwan

O-17

"**A Hybrid Optical / Photoacoustic Microscopic System with Novel Deconvolution Processing for Morphological and Functional Cellular Imaging**"

Ryo Shintate

Tohoku University, Japan

O-18

"**Development of strong and ductile high entropy alloys for biomedical applications**"

Daixiu Wei

Tohoku University, Japan

O-19

"**Lymph node metastasis mouse model and its treatment**"

Ariunbuyan Sukhbaatar

Tohoku University, Japan

Closing address (12:15–12:20)

Takao HANAWA, Tokyo Medical and Dental University, Japan

Session I

Oral Health Care

Multifunctional Biomaterials for Smart Wearable Healthcare Devices

Sei Kwang Hahn[1,2*], Geon-Hui Lee[1], Su-Kyoung Kim[1], Sangbaie Shin[2]
[1] *Department of Materials Science and Engineering, POSTECH, Pohang, Korea*
[2] *PHI BIOMED Inc., Seoul, Korea*

Recently, numerous diagnostic and therapeutic devices are routinely used in the clinic including ocular and dental applications. While these devices have a familiar look wall-plugged in hard packages and placed at patient's bedside, there have recently been a rapid expansion of new ideas on various wearable functional devices. This innovation is fueled by the development of a variety of enabling multifunctional biomaterials. Among various wearable devices, a smart contact lens is especially noticeable for healthcare applications, because it can be used as an excellent interface between the human body and an electronic device. Here, we developed smart contact lens and smart wearable device for both continuous diabetic monitoring and diabetic retinopathy therapy. Smart contact lens could measure tear glucose levels as a non-invasive alternative to the conventional blood glucose tests and deliver drugs from gold coated reservoirs for the treatment of diabetic retinopathy. On the basis of these results, we also developed a smart wearable device for highly sensitive glucose monitoring in sweat for clinically feasible diabetic diagnosis. A blue-tooth system could send data wirelessly allowing patients to check their diabetic diagnosis results on the mobile phones. Furthermore, we developed a NIR light emitting contact lens for the diabetic diagnosis and the treatment of diabetic retinopathy based on photobiomodulation. The retinal vascular hyper-permeability induced by diabetic retinopathy in rabbits was reduced to the statistically significant level by simply wearing the NIR light emitting contact lens. This presentation will showcase the current state-of-the-art smart contact lenses and other wearable devices for mobile healthcare and personalized medicine.

[1] S. K. Hahn et al., Nature Reviews Materials, 5, 149-165 (2020).
[2] S. K. Hahn et al., Science Advances, 6, eaba3252 (2020).
[3] S. K. Hahn et al., Advanced Materials, 30, 1701460 (2018).
[4] S. K. Hahn et al., Nature Communications, 7, 10374 (2016).
[2] S. K. Hahn et al., Nature Photonics, 7, 987-994 (2013).

Effect of Ta Addition on the Antibacterial Activity and Cytotoxicity of Ag-containing Amorphous Calcium Phosphate Coating Film

Kyosuke Ueda[1], Jun Wu[1], Koyu Ito[2], Kouetsu Ogasawara[2], Maiko Furuya[3], Kotone Yokota[3], Hiroyasu Kanetaka[3], Takayuki Narushima[1]

[1]*Dept. of Materials Processing, Tohoku University*

[2]*Dept. of Immunobiology, Institute of Development, Aging and Cancer, Tohoku Univ.*

[3]*Liaison Center for Innovative Dentistry, Graduate School of Dentistry, Tohoku Univ.*

Since surgical site infection caused by bacteria is one of the serious complications associated with bone substitutional implants, the surface of the implants requires not only the bone compatibility but also antibacterial property. In our previous study, amorphous calcium phosphate (ACP) coating films were fabricated on Ti implant using RF magnetron sputtering and the ACP coating films improved the bone formation of the Ti implant because of their dissolution[1]. Ag is known as an antibacterial element and the dissolved Ag ions kill the bacteria. However, controlling the Ag ion release from the surface of the devices is important because excess Ag ion release also kills the cells. To archive both bone compatibility and antibacterial property, we fabricated Ag-containing ACP (Ag-ACP) coating films[2]. In this study, Ta was co-contained in the Ag-ACP coating films to control the dissolution of Ag and the effect of Ta contents on the antibacterial activity and cytotoxicity of the Ag-ACP coating films was evaluated.

Ag-ACP coating films containing without and with low and high Ta contents were fabricated by RF magnetron sputtering on blasted Ti-6Al-4V substrates (Ag-ACP, (Ag+L-Ta)-ACP, (Ag+H-Ta)-ACP). The thickness of the coating films was 0.5 μm. A diluted nutrient broth (NB) solution (an 80-fold dilution of NB by purified water) was used for the antibacterial test (ISO 27447). A specimen was incubated in 5 mL of *E. coli* suspension with an initial concentration of 1×10^7 CFU·mL^{-1} in the diluted NB solution. After incubation for 10.8 ks, the number of viable *E. coil* was less than 1 for all Ag-containing ACP coating films, and Ag ions were detected from all suspensions after the antibacterial tests indicating antibacterial activity. The amount of released Ca and P-related ions decreased with increasing Ta concentrations in the coating films after 86.4 ks incubation in the suspension. This suggests that the addition of Ta is effective in suppressing the dissolution of the Ag-containing ACP coating films.

Cytotoxicity of the coating films was evaluated using V79 cells with direct and indirect methods (ISO 10993-5). Although the (Ag+L-Ta)-ACP coating films showed cytotoxicity, no cytotoxicity was observed from the (Ag+H-Ta)-ACP coating films. (Ag+H-Ta)-ACP coating film remained even after immersion in the bacterial suspension.

These results indicate that the (Ag+H-Ta)-ACP coating films show long-term antibacterial activity and no cytotoxicity because of the well-controlled Ag ion release.

References

[1] S. Yokota, K. Ueda et al.: Implant Dentistry, 23 (2014) 343–350.

[2] J. Wu, K. Ueda et al.: Mater. Sci. Eng. C, 109 (2020) 110599.

Periodontitis-associated bacterial culture supernatants inhibit the glucose metabolic activity of host cells.

Haruki Otani[1,2] , Jumpei Washio[1] , Satoru Yamada[2] and Nobuhiro Takahashi[1]
[1]*Division of Oral Ecology and Biochemistry, Department of Oral Ecology, Tohoku University Graduate School of Dentistry, Sendai, Japan*
[2]*Division of Periodontology and Endodontology, Department of Oral Ecology, Tohoku University Graduate School of Dentistry, Sendai, Japan*

Introduction: Periodontitis is one of the major oral diseases, and most Japanese adults suffer from this disease. Periodontitis causes the destruction of periodontal tissues and subsequent tooth loss. The pathogenesis of periodontitis has been investigated by many previous studies; however, the onset of periodontitis, especially the direct effect of periodontitis-associated bacteria on periodontal tissues is still unclear. Therefore, in this study, we investigated the effects of culture supernatants of *Porphyromonas gingivalis*, one of the representative periodontitis-associated bacteria, on host cells using glucose metabolic activity as an essential and sensitive indicator of cell activity.
Materials and Methods: We used *Porphyromonas gingivalis* wild-type strain ATCC33277 (WT) and gingipain-defective mutant KDP136 (GM). As host cells, HaCaT (human skin keratinocyte) cells were used. These bacterial strains were grown anaerobically and the culture supernatants were collected. The effects of the culture supernatants on the glucose metabolic activity of the host cells were evaluated. To measure the glucose metabolic activity of host cells, we used a pH-stat system that can monitor the amount of acid produced by host cells through their glucose metabolism. The organic acids in the culture supernatants were analyzed with HPLC, and the effects of organic acids on host cells were also examined similarly.
Results and Conclusion: The glucose metabolic activity of HaCaT was significantly inhibited only by the culture supernatants of WT. On the other hands, organic acids detected in supernatants of WT did not affect the glucose metabolic activity. Furthermore, heated or filtered culture supernatants of WT had no effect. These results suggest that WT-derived gingipain or gingipain-associated proteins inhibit the glucose metabolism of host cells. Further studies are needed to identify the molecules involved in metabolic inhibition.

TNF-α Directly and Indirectly Induces RANKL Expression on Osteocytes during Orthodontic Tooth Movement

Fumitoshi Ohori, Hideki Kitaura, Aseel Marahleh, Saika Ogawa, Takahiro Noguchi, Yasuhiko Nara, Adya Pramusita, Ria Kinjo, Jinghan Ma, Kayoko Kano, Itaru Mizoguchi

Division of Orthodontics and Dentofacial Orthopedics, Tohoku University Graduate School of Dentistry, Sendai, Japan

[Background] Orthodontic tooth movement occurs by bone remodeling with osteoclastic bone resorption on the compression side and osteoblastic bone formation on the tension side. Osteocytes express RANKL and have a major role in osteoclast formation during orthodontic tooth movement. Tumor necrosis factor-α (TNF-α) is also important in osteoclast formation during orthodontic tooth movement as TNF receptors deficient mice exhibited less tooth movement than C57BL/6J mice. Several studies suggested that sclerostin expressed by osteocytes promoted bone remodeling via RANKL expression in osteocytes. However, the effect of TNF-α on the expression of RANKL and sclerostin in osteocytes during orthodontic tooth movement remains unclear. [Objectives] The objectives of this study are to investigate the effect of TNF-α on RANKL and sclerostin expression in primary osteocytes and to examine how TNF-α affects RANKL and sclerostin expression in osteocytes during orthodontic tooth movement. [Methods] For *in vitro* analysis, neonatal Dmp1-Topaz transgenic mice, which osteocytes express the topaz variant of the green fluorescent protein (GFP), were used to isolate primary osteocytes through cell sorting. Primary osteocytes were incubated with TNF-α or sclerostin, gene expression levels were analyzed by real-time RT-PCR. For *in vivo* analysis, PBS or TNF-α was subcutaneously injected into the C57BL/6J mice calvariae part, once daily for 5 days, to evaluate RANKL and sclerostin expression on osteocytes by immunohistochemistry. As an orthodontic tooth movement model, a Ni-Ti closed-coil spring connecting the upper incisors and upper-left first molar was attached to move the first molar to the mesial direction in C57BL/6J mice and TNF receptors deficient mice. RANKL- and sclerostin-positive osteocytes on the compression side of the distobuccal root of the upper-left first molar were evaluated by immunohistochemistry. [Results] *SOST* mRNA expression, which encodes sclerostin, increased when osteocytes were cultured with TNF-α. In addition, *RANKL* mRNA expression increased when osteocytes were cultured with TNF-α or sclerostin. The percentage of RANKL- and sclerostin-positive osteocytes were higher in the calvariae of TNF-α injection group. The percentage of RANKL- and sclerostin-positive osteocytes on the compression side of the first molar in TNF receptors deficient mice was lower than that in C57BL/6J mice after orthodontic tooth movement. [Conclusion] These results suggest that there are two pathways of osteocytes for osteoclast formation during orthodontic tooth movement: TNF-α directly enhances RANKL expression on osteocytes, and TNF-α indirectly enhances RANKL expression via sclerostin expression on osteocytes. We concluded that TNF-α plays an important role in RANKL and sclerostin expression on osteocytes and promotes osteoclast formation on the compression side during orthodontic tooth movement.

Session Ⅱ

IDEA
(Innovative Dental-Engineering Alliance)

Birefringence as a proxy for viscoelastic properties of cartilage using polarisation sensitive optical coherence tomography

Frédérique Vanholsbeeck*[a,b], Matthew Goodwin[a,b], Marie Klufts[a,b], Joshua Workman[c], Ashvin Thambyah[c]

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Non-invasive determination of structural changes in articular cartilage is paramount for osteoarthritis researcher and clinician alike as it allows us to identify, understand and evaluate articular cartilage damage that could lead to osteoarthritis (OA). Slow degeneration and injury result in degenerative and traumatic OA respectively. Using polarisation sensitive optical coherence tomography (PS-OCT), we have investigated both OA types on the bovine and the equine models. While previous studies have shown that PS-OCT presents a useful real-time non-invasive tool for to studying cartilage morphology and detecting osteoarthritic changes, it has limited ability to quantify the subtle changes in the early stages of joint degeneration. In our studies, we have applied a range of processing methods to OCT images taken during compression or post and pre-impact for detecting microscale degenerative changes in cartilage and for defining structurally relevant metrics required for understanding the mechanical factors of osteoarthritic initiation and progression.

Biography

After a two year stint in architecture, I studied physics at the Université Libre de Bruxelles (Belgium). In 2003, I got my PhD as well as a diploma in teaching (secondary). I then moved to New Zealand and have been at The University of Auckland ever since. In 2005, I started an experimental biophotonics research group to develop novel imaging technologies. My research team is now strong of twelve people from all over the world. My research interests span from counting bacteria for food safety and antibiotics testing, to detecting early signs of diseases using optical coherence tomography.

Haptic interaction with deformable objects and various materials based on physics simulations

Shoichi Hasegawa[1], Haiyang Ding[1]

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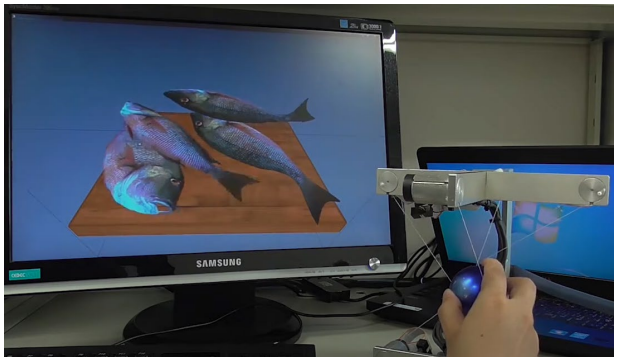
In this talk, we introduce two haptic interaction systems. The first one realizes probing haptic interactions with deformable objects in a multirate haptic rendering system.

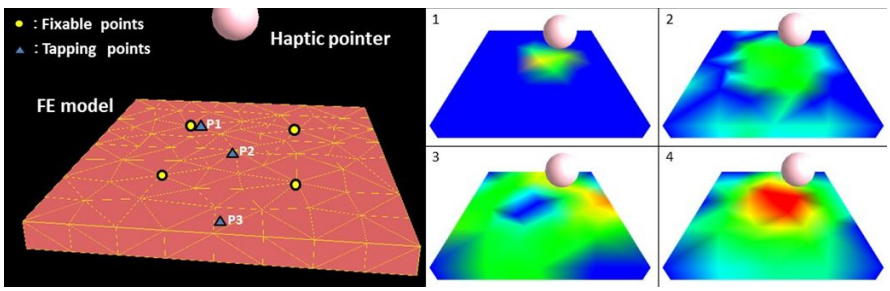
Most haptic systems suffer from what is known as the “tunneling” problem, which arises when a virtual object moves or deforms largely towards a small virtual tool. This problem occurs because the displacement of the virtual object is not considered during collision detection and can be solved with Continuous Collision Detection (CCD). Originally, haptic rendering with CCD was proposed for applications with 6 Degrees-of-Freedom (DoF) only.

On the other hand, 3-DoF spherical probe is more sutable for applications probing deformable objects with complex surfaced shapes and feeling the shapes and deformation. The system here realizes 3-DoF spherical probe, which eliminate the "tunneling" problem, with complex surface shaped objects by using combination of particle based deformation model and mesh based surface model.

The second one present material feel by simulation and feedbacks of vibration when tapping. A modal analysis of finite element model of object generate waveform of vibration which occurs when the user taps a point on the object. By adding the waveform of the vibration to the surface normal forces, realistic waveform of a feedback force is reproduced and give material feel to the user.

Both system utilize a tension based haptic interface SPIDAR, which transmit a wide bandwidth feedback force to the user's hand. Recent progress of simulation and computation techniques realize realistic feel and interaction.





Comparative study of capacity of protein adsorption onto octacalcium phosphate prepared by different synthesis conditions

Ryo Hamai, Kaori Tsuchiya, Susumu Sakai, and Osamu Suzuki

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Octacalcium phosphate (OCP) has been applied as an artificial bone substitute material. The hydrolysis of OCP through the incorporation of Ca^{2+} and the release of inorganic phosphate (Pi) ion induces osteoblastic differentiation and osteoclast formation *in vivo* and *in vitro*.[1)] We reported that OCP coprecipitated with gelatin (c-OCP) can be prepared based on a wet synthesis method.[2)] It was also demonstrated that c-OCP/gelatin sponge composite exhibited distinct bone regeneration ability and biodegradability in various bone defect models.[3,4)] However, it is still unclear how coprecipitated gelatin molecules affect the solubility of OCP crystals concomitant with the enhancement of biodegradability. On the other hand, it was reported that protein adsorption suppressed the dissolution of OCP in physiological condition.[5)] In the present study, the capacity of serum protein adsorption onto OCP crystals prepared in the presence (c-OCP) or the absence (w-OCP) of gelatin was examined *in vitro*.

w-OCP and c-OCP crystals were prepared by the wet synthesis method based on the previous report.[6)] c-OCP was synthesized in the presence of 0.5 wt.% gelatin under the degree of supersaturation with respect to OCP.[2, 3)] The precipitated w-OCP and c-OCP were separated from the reaction solutions and then washed, before drying. Tris(hydroxymethyl)aminomethane-HCl buffers containing 0.5 mM Ca^{2+} and 0.5 mM Pi ion and bovine serum albumin (BSA) ranging from 0 to 0.75 mg/mL were prepared for the adsorption test. The solution pH was adjusted to 7.4 at 37°C. These BSA solutions were saturated with respect to OCP. The w-OCP and c-OCP granules were incubated in the BSA solutions for one hour at 37°C. After the incubations, the supernatants were obtained by the centrifuge. The BSA concentration in the supernatants was determined with a CBB protein assay. The ion concentration in the supernatants was also measured by testing kits. The collected w-COP and c-OCP before and after the incubations were analyzed using Raman spectrometry.

The typical peaks corresponding to HPO_4 and PO_4 in OCP structure were observed in Raman spectra for w-COP and c-OCP before and after the incubations regardless of BSA concentration. The peaks attributed to the remained gelatin were also detected in Raman spectra of c-OCP after the incubations. The isotherms determined by BSA concentration in the supernatants indicated that the adsorption amount of BSA onto w-OCP was higher than that onto c-OCP. Pi ion concentration in the incubated BSA solutions was changed by the BSA concentration and synthesis condition of OCP. These results suggest that the co-precipitation of gelatin could affect the solubility of OCP by regulating the serum protein adsorption onto the surface of crystals.

References

1) O. Suzuki. *Jpn Dent Sci Rev* 49: 58-71 (2013). 2) T. Handa et al. *Acta Biomater* 8: 1190-1200 (2012). 3) R. Ishiko-Uzuka et al. *J Biomed Mater Res B Applied Biomater* 105: 1029-1039 (2017). 4) S. Chiba et al. *J Biomed Mater Res A* 104: 2833-2842 (2016). 5) T. Masuda et al. *Biomater Appl* 31: 1296-1304 (2017). 6) O. Suzuki et al. *Tohoku J Exp Med* 164: 37-50 (1991).

Binary Malignancy Classification of Skin Tissue using Reflectance and Texture Features from Macropathology Multi-Spectral Images

Takashi OBI[1], Eleni ALOUPOGIANNI[1], Hiroyuki SUZUKI[2], Takaya ICHIMURA[3], Atsushi SASAKI[3], Hiroto YANAGISAWA[3], Tetsuya TSUCHIDA[3], Masahiro ISHIKAWA[3], Naoki KOBAYASHI[3]

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Skin lesion treatment begins with macropathology, which refers to the initial examination of excised tissue specimens, prior microscopic evaluation. Usual protocol requires compilation of a report describing gross features and photographs of specimens to map dissection sites after formalin fixing and bread-loafing. Relevant gross features are upheld by changes in shape, size, color or texture, while melanoma detection employs the commonly referred as ABCDE macroscopic descriptors (asymmetry, border, color, diameter, evolution). The pathologist's goal during initial biopsy is to accurately identify critical tissue areas on the specimen and assess the condition of their margins, in order to determine whether further ablation is required. A major concern in macropathology is protocol and equipment discrepancies among different pathology laboratories. Specifications of the camera system, image acquisition algorithm, scene illumination and display device are factors which cause color variation in the resulting image. Imaging quality is essential for effective pathology, taking into account that in many instances a second evaluation is necessary. Furthermore, macropathology is dependent on the age, training and experience of the physician, while lacking standardization and automation as a procedure. Consequently, it is time-consuming and produces high workload for the pathology laboratory. In the advent of digital pathology, macropathology remains an impractical task.

Multi-spectral images (MSI), an enhancement of the RGB format, can alleviate obstacles in image quality and color reproduction through the use of narrow band filters, expressing a spectral dimension. MSIs exhibit higher sensitivity to image features that are masked in RGB images, additionally, MSI is preferred for retrieving spectral surface reflectance of objects compared to RGB. Machine learning classification at dermatologist level based on conventional or multispectral images has been already investigated with favorable accuracy. However, macropathology images are generally neglected, with current focus being on multispectral digital slide images for histological analysis, improvement of color validity and cancer tissue classification. By applying traditional machine learning techniques on macropathology MSI (macroMSI) of excised skin tissue, this study aims to investigate automatic classification of tissue malignancy and provide a visual tool for diagnosis that performs in a consistent manner independently of capturing conditions.

We propose a novel quasi-automated framework based on color and texture analysis of macroMSI, capable of classifying malignancy of critical regions on excised tissue in order to assist margin identification for skin cancer in current macropathology practice. Our approach attempts to mimic the pathologists' assessment of color and texture, by combining hand-crafted features from reconstructed spectral reflectance and local binary patterns, respectively.

Session Ⅲ

Biomaterials

Utilisation of Ceramic films in Biomedical and Environmental Applications

Masato Ueda[1], Masahiko Ikeda[1]

[1] *Faculty of Chemistry, Materials and Bioengineering, Kansai University*

Functional ceramics are employed in various fields because they show characteristic physical and chemical properties. The role of ceramics changes depending on purposes and applications even in the same materials. For examples, titanium dioxide was used for control of (a) bone conduction, (b) cell adhesion or coral reef restoration.

(a) Control of bone conduction

Titanium and its alloys have been used widely as biomaterials for orthopaedic implants because of their excellent mechanical properties and biocompatibility. However, the alloys don't show significant characters in bone conduction. Therefore the bone conduction should be improved when these alloys are employed in hard tissue substitutes. In contrast, it should be suppressed when these alloys are employed in bone plates/screws which are removed after recovery. TiO_2 and TiO_2-ZrO_2 films were synthesised on pure Ti by combined chemical-hydrothermal treatments, and then the samples were implanted into tibiae of eight-week-old rats. Contact ratios between cortical bone and implant were measured to be 47% and 24% on TiO_2 and TiO_2-ZrO_2 films, respectively. TiO_2 drastically promoted the bone conduction. On the other hand, bone conduction is known to be suppressed on metallic Zr. In the TiO_2-ZrO_2 film, the small amount of ZrO_2 effectively worked on it.

(b) Control of cell adhesion

Several techniques have been employed to attach/detach cells to/from a substrate. Cells cultured on a substrate are generally detached from the substrate into a sheet by the destruction of protein between the cells and the substrate using enzymes such as trypsin. However, the enzymes also damage the adhesion molecules among the cells. TiO_2 is an n-type semiconductor with an energy band gap of 3.2 eV, which displays a photocatalytic activity under ultraviolet light (UV). Basically the number of cells monotonically increased with incubation periods under darkness on TiO_2. Previous light irradiation promoted the cell adhesion on the surface. In contrast, the cells decreased under continuous light irradiation. Surface potential could be locally controlled by local light irradiation. The cells were confirmed to adhere preferentially on the dark region. The results imply that the adhesion/proliferation/detachment behaviours of cells can be controlled locally by the photo-responses of TiO_2 and the irradiation patterns.

(c) Coral reef restoration

In vertebrates such as mammals, osteoblast is known to produce type-I collagen molecules and then hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, is precipitated on the fibres from blood plasma. Corals have osteoblasts in polyps on the surface of skeletons. They secrete organic matrix similar to the collagens and it triggers the precipitation of calcium carbonate, $CaCO_3$ from seawater. Thus, they have very interesting analogy in the formation process of bone and coral skeletons though the materials of skeletons are different. Then the coral fragments were reared on TiO_2 synthesised by the anodic oxidation of pure Ti. The colony of polyps vigorously expanded on the surfaces of TiO_2. In addition, formation of coral skeleton was clearly observed on the TiO_2.

Improvement of osteoconduction of preosteoblast by titanium with patterned periodic nano surface topography fabricated by femtosecond laser irradiation

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The next generation surface modification on medical and dental implants is coatings of tissue or stem cells on them[1]. To promote cellular attachment and formation of tissues on materials, the control of patterned surface topography is necessary. For example, a titanium (Ti) surface with nano topography regulates cell attachment and promotes osteogenic differentiation[2-3], on the other hand, a limit cell proliferation was observed, simultaneously[4]. To study the role of periodic nano topography on the biocompatibility and osteoconductivity of metallic biomaterials, we investigated adhesion, proliferation and calcification of mouse preosteoblastic cells (MC3T3-E1) to Ti with three patterned periodic nano-ripples surface topographies fabricated by femtosecond laser irradiation.

Ti disc with mirror-polished surface (mTi, grade 2) was scanned with a femtosecond laser[3]. As a result, Ti surfaces with three patterned nano topography were fabricated: full-surface topography (fTi), half-surface topography (hTi), and checkboard-patterned topography (cTi). The chemical state of Ti surfaces with and without laser irradiation was characterized using XPS, and it showed that there was no significant difference of surface compositions and chemical states among Ti specimens with and without laser irradiation. The initial cell extension morphology was visualized by fluorescent staining, where a highly aligned cellular morphology was observed with cells cultured on Ti with nano surface topography. The proliferation of cells cultured on each specimen was evaluated by determining the number of attached cells using Cell Counting Kit-8[4]. Compared with mTi and fTi, larger number of attached cells was detected with hTi and cTi, which indicated an improved a cell growth rate. The osteogenic differentiation was induced with induction medium and calcification of MC3T3-E1 cultured on Ti surfaces was evaluated with alizarin red S staining[3]. Compared with mirror surface, cells cultured on the periodic nano surface topography showed a larger calcified area, which indicated superior osteoconductivity. Notably, the chessboard-patterned Ti surface showed a better balance between proliferation and calcification, which is expected to provide a basis for designing novel biomaterial–cell interfaces to improve the osteoconductivity of metallic biomaterials for medical and dental implants.

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The effect of cryogenic thermal cyclic processing on the mechanical properties of TiNi based crystalline/amorphous alloy

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TiNi based bulk metallic glass (BMG) composites which have dual crystalline and amorphous phases were fabricated with excellent mechanical properties, combining a fairly strain of 20% in ductility and a high stress of 2300 MPa in strength. Two crystalline phases are observed in the as cast state, the austenite B2 phase is the dominant phase and a small amount of martensite B19' phase which was formed by the restriction of amorphous phase. The reversible phase transform between the martensite and austenite could be induced by both thermal and stress. Considering the rejuvenation of amorphous phase by the cryogenic thermal cycling between room temperature (R.T.) and liquid nitrogen temperature (77 K), we explored synthetic effects for the TiNi crystalline/amorphous alloy by the thermal cycling treatment.

After performing the cryogenic thermal cycling on TiNi crystalline/amorphous alloy, the critical stress (σ_m) for martensitic phase transformation and the young's modulus display increase in the compressive deformation, while it shows opposite behaviors by the low cycle mechanical fatigue effect. The cryogenic thermal treatment activates the initial martensite phase which is restrict by the amorphous phase and enables the as-quenched martensite transform into the high temperature stable austenite phase. During the thermal cycling the amorphous work coefficient with the crystalline phase transformation and the fraction of martensite phase reduces. On the other hand, the microstructure changes during the thermal treatment crystal phase and the amorphous phase formed a lamellar structure. These effects induce a activation energy changing which could be calculated by the DMA analysis, and responsible for the increases of critical phase transformation stress by the cryogenic thermal cycling treatment.

Keywords: TiNi composite alloy, Cryogenic thermal cycling, mechanical properties

Physical properties of Ti-36Nb-2.0Ta-3.0Zr-0.35O alloy prepared by powder metallurgy

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Ti-Nb-Ta-Zr-O(TNTZO) alloy after large deformation for biomedical applications has become the research hotspot due to its excellent properties, including high strength, room temperature super-plasticity, low work hardening rate and superplasticity etc. In this work, Ti-Nb-Ta-Zr-O alloy bars, wires, and plates were successfully prepared by powder metallurgy and plastic deformation; the microstructural evolution during the preparation process and mechanical properties of TNTZO alloy at room and cryogenic temperatures were investigated systematically. The alloy after cold swaging by 85%, shows the typical "marble-like" structure with α" phase induced by stress and the TNTZO alloy wire after cold drawing shows nanocrystalline structure. The plastic deformation behavior of the alloy is sensitive to test temperature and cold deformation history of the alloy. For the alloy without cold deformation, both tensile strength and ductility have a significant enhancement at cryogenic temperatures, mainly due to the occurrence of mechanical twinning. For the alloy cold swaged by 85%, an increase in strength accompanied by a decrease in uniform elongation is found at cryogenic temperatures. Besides, pre-deformation was applied to TNTZO alloy with the hope of improving its overall mechanical properties. With the increase of pre-deformation reduction, the increase of β phase stability causes the decrease in the amount of {332}<113> deformation twinning, the increase in that of {112}<111> deformation twinning and the occurrence of slip bands. The enhanced twinning activities in alloy pre-deformed by 9% and 15% contribute to the strain hardening and the enhanced ductility.

Microstructure evolution and deformation behavior of graphene oxide induced TiC reinforced Ti6Al4V processed by friction stir processing

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As a joint implant material, wear resistance and surface strength of Ti6Al4V alloy need to be further enhanced. Friction stir process (FSP) can form hard stir zone with ultrafine grains, and graphene oxide is a good source for generating wearable TiC. Combination between FSP and TiC reinforcement is a promising way to obtain a performance improvement. This work investigates microstructure evolution and deformation behavior of graphene oxide induced TiC reinforced Ti6Al4V processed by friction stir processing. XRD, SEM, TEM are used to analyze phase content and characteristics. Nanoindentation and micro-pillar compression are processed to learn deformation mode during compression loading. TiC inherits shape of graphene oxide and forms as nanoband instead of particle. Despite the nano size, twin structure is observed in TiC band and has specific orientation with hcp alpha matrix. TiC nanotwins show a strengthening effect at shallow stir zone and compensate for deformation adaptation resulted from alpha twins. Recrystallization in shallow stir zone is slightly restricted by TiC nanotwins and weak gradient texture is obtained in stir zone. Stress-induced martensitic transformation is suppressed in stir zone. This research may open new frontiers in the design of nanoscale surface structure of biomaterials.

Session Ⅳ

Industry-academia-government collaboration

Entrepreneurship from University Seeds and Second Foundation

Shimpei Sato

[1]*Acuity inc. CEO CTO*

I will look back and introduce the process of starting a business and growing an organization from a university's needs.

(1) Business that arose from requests and ideas from Tohoku University
(2) Entrepreneurial History
(3) Post-startup growth and transformation
(4) Becoming Sophisticated Competence
(5) Digital Transformation Business Initiatives
(6) Starting and running a business

Effect of oxygen content on the melting behavior of stainless-steel powders for laser additive manufacturing

Weiwei Zhou, Naoyuki Nomura

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【Introduction】 Laser powder bed fusion (L-PBF), as a newly developed additive manufacturing technology, has attracted increasing attention in the field of biomaterials, and aerospace. Compared with traditional methods, L-PBF provides many advantages, such as the direct production of complex shapes, high material utilization rate. Unfortunately, even though the non-melted powders can be recycled for decreasing cost during L-PBF, it is necessary to pay attention to the oxidation problem of used powders. The oxygen content may influence the melting behavior of powders due to high melting points of oxides, and thus the mechanical properties of builds will be decreased. Thus, there is an empirical operation of discarding the metallic powders after using several times. However, the effect of powder oxidation on the quality of final L-PBF products has not been understood so far. In this work, therefore, we intentionally prepared the oxidized powder and performed L-PBF process. The effects of oxygen content on the builds was examined from the viewpoints of the characteristics and melting behavior of powders, as well as the microstructure and mechanical properties of L-PBF builds.

【Experimental】 Firstly, gas-atomized SUS316L powders were respectively oxidized at 400℃ and 500℃ for 2 h in air. The laser absorptivity, flowability, phase constitution, and melting points of raw or oxidized powders were evaluated. Subsequently, L-PBF process was performed for raw or 500 ℃-oxidized powders with different building parameters. The appearance, relative density, microstructure, and mechanical properties of L-PBF builds were analyzed and compared.

【Results and discussion】 The laser absorptivity of SUS316L powders increased from 66.1% to 67.3% or 73.3% after oxidation at 400℃ or 500℃, respectively; whereas their melting points were almost the same. After L-PBF, the surface of builds using 500℃-oxidized powders was darker than that using raw powders. Oxygen-rich stripes were confirmed at the boundary of beads on the surface of both builds, while the stripe width was larger in the builds using oxidized powders. The relative density of two kinds of builds increased with increasing applied energy density. However, the builds using oxidized powders showed higher relative density at low energy density. Moreover, the elongation of the builds using oxidized powders was lower than that using raw powders, while the UTS and 0.2% proof strength did not change. An oxide layer with the thickness of ~ 20 nm was formed simultaneously on the 316L build.

Nanomodification of dental implants to improve its mechanical and biological performance

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In recent years, considerable advances in the field of medical materials have begun to emerge. The modern area of nanostructured implants possesses wide applications in various medical implants including its dental use. Nano-surface functions and nanomodification techniques are among the modern solutions to solve the medical challenges through improved biomaterial performance, innovative dental-implant designs, and modern surface design procedures. Some of these procedures can be named as nanoscale adhesive surfaces, utilization of bio-chemical anodization, and surface modification techniques. This work covers the nanotechnological advances and its development in dental implants and includes a description, basic properties, and the related results of composites and surface morphologies, and the different types of nanomaterials used in dental implants. Recently, researchers are specially focused on strengthen the osteointegration of dental implants and to prevent bacterial adhesion and biofilm formation on the implant surfaces. The micro and nano-topography of the implant surface, control the biological reactions of implants hence its tailoring can solve the problems associated with implant-tissue issues. This research offers a brief description of the nanostructured biomaterials in dental implant application in order to enhance their biological and mechanical performance and may open new frontiers in the progression of dental implant technology.

Sulfobetaine polymer conjugates for anticancer drug delivery to cell spheroids

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In vitro three-dimensional cell aggregates (spheroids) have attracted attention in the fields of drug screening and regenerative medicine because of the better construction of in vivo microenvironments than two-dimensional monolayer cultures. However, the efficient drug delivery with permeation to the inside of spheroid is essential for further usage of spheroids. Nanocarriers with high permeability to spheroids aimed at application were also studied in recent years, but these nanocarriers are still developing. We prepared a random copolymer containing sulfobetaine unit, poly(3-dimethyl(methacryloyloxyethyl)ammonium propanesulfanate)-*ran*-poly(ethyleneglycol methacrylate), P(DMAPS-PEGMA), as a biocompatible nanocarrier. In this study, we modified the P(DMAPS-PEGMA) by anticancer drugs (Doxorubicin, 17-AAG) and added to human glioblastoma A-172 cell spheroids. We analyzed the translocation behavior into spheroids and evaluated the drug efficacy against the spheroids.

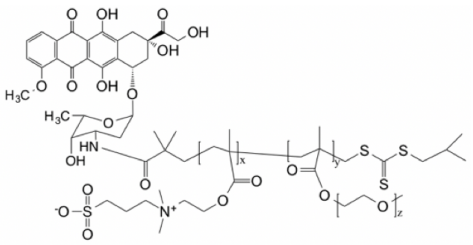

Figure 1 Chemical structure of Dox-P(DMAPS-PEGMA)

The fluorescence of Dox-P(DMAPS-PEGMA) was observed the gradual permeation from the outer side of spheroids and observed from the center of spheroids after 1-2 h incubation. On the other hand, Doxorubicin permeated only 2 – 3 cell layers from the outer side. Interestingly, the Dox-P(DMAPS-PEGMA) was localized in mitochondria in both spheroids. Dox-P(DMAPS-PEGMA) showed the drug efficiency even after the conjugation and significantly inhibited the growth above 3 μM, however, the effects of growth inhibition was a bit lower than that of Dox. On the other hand, 17-AAG-P(DMAPS-PEGMA) exhibited remarkable effect of prevention from the growth and invasion of A-172 cell aggregates. The complete inhibition was accomplished at 0.3 μM. The drug efficacy was ~10 fold higher than 17-AAG itself. Improvement of the solubility and localization might affect by conjugation with P(DMAPS-EPGMA). Conjugation with such sulfobetaine copolymer will open doors for drug screening, regenerative medicine, etc.

Session Ⅴ

Young innovators' session

Viewpoints on R&D of innovative biodegradable Mg alloys from the aspect of accelerating clinical transformation

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Biodegradable magnesium alloys have been widely studied for more than ten years, and great progresses have been achieved with the efforts of scientists from all over the world, including new alloys, new coatings and in vivo evaluations. However, by far few could finally achieve clinical transformation. We could say that the lagging Registration and Approval policy is part of the reason, especially for revolutionizing biomaterials. But on the other hand, is there anything we could do regarding of R&D process to accelerate the clinical transformation? Before a new metallic alloy was registered for clinical trial, it usually went through several processes including alloying design and fabrication, mechanical properties, in vitro degradation test, cytocompatibility evaluation, animal experiments, etc., which is a system engineering. And how to optimise and plot the whole process will be critical. In this talk, the lecturer would share his own experiences and thoughts on how to make the R&D process more effectively, including how to design the novel biodegradable Mg alloys based on the clinical requirements and how to arrange the biological evaluation including animal experiments. At last, the lectures would like to discuss on how and when to involve the clinicians and company in the R&D to accelerate the whole process.

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Nonlinear resonance of a ball-impact electromagnetic energy harvester for low frequency vibration

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The nonlinear resonance of a cantilever beam under mechanical impacts is investigated experimentally for potential energy harvesting from human induced low-frequency vibrations. In our prototype, a metal ball is used to yield impulsive forces acting upon a cantilever installed in an electromagnetic type vibration energy harvester. A multipole magnet array attached on the cantilever moves above a planar coil fixed on the baseplate of the device, leading to power generation through electromagnetic induction. Due to the nonlinear excitation force arising from ball impacts, superharmonic resonance occurs at integer fractional frequencies of the cantilever's natural frequency. The nonlinear response amplitudes of the cantilever and resulting induced voltage have been measured under continuous sinusoidal excitation at 1-20 Hz. To explore the resonance characteristics, we have examined three cantilevers with different natural frequencies: 21, 34 and 76 Hz. In addition, the travelling distance of the ball has been varied to realize the maximum induced voltage. It is found that the travelling distance needs to be tuned depending on the natural frequency of the cantilever since there is an optimal distance for power generation. For larger travelling distances, the induced voltage decreases. The critical distance can be numerically estimated by using a mechanical model based on a single degree of freedom damped mass-spring system. The combination of the frequency up-conversion technique and the tuning strategy developed in this study offers a fundamental advantage for optimizing low-frequency vibration energy harvesting using compact device dimensions when compared to other commonly used on-resonance harvesters.

Developments of Flexible and Biocompatible Hybrid Materials towards the Glucose Sensing Applications

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[Developments of flexible, wearable, and biocompatible devices]

The preparations and characterizations of the flexible silk–Pt composite materials for the applications towards the wearable and medical devices have been studied in this work. Supercritical carbon dioxide (sc–CO_2) was introduced into the electrochemical process for enhancing the adhesion between silk and Pt as well as smoothen the Pt metallization layer. Metal ions, which were released into the simulated body fluid (SBF) in the immersion test, were negligible while comparing to the daily metal input and output of human body. The hybrid materials showed high corrosion resistances in both 3.5 wt.% NaCl and SBF solutions (Fig. 1). The electrical conductivity and corrosion resistance persisted after the adhesion tests. The aforementioned evaluations revealed the practicability of this flexible silk–Pt composite to wearable and medical devices.

[Enhancement of glucose sensing]

Electrode materials for the glucose sensing have become a crucial issue in biomaterials owing to the growth of population in diabetes mellitus. The materials for glucose sensors thus have been widely studied; nano–metal and/or nano–oxide have been reported to perform remarkable electrocatalytic activities in the non–enzymatic glucose sensors. In this study, an Au nanoparticles (NPs)–TiO_2 tailored polyaniline (PANI) composite was realized for the applications of the non–enzymatic glucose sensors (Fig. 2). Electrode with the trade–off between Au NPs and TiO_2 nanoparticles performed the highest electrocatalytic activity to the oxidation of glucose. The sensitivity and detection limit were 379.8 μA mM^{-1} cm^{-2} and 0.15 μM, respectively. High selectivity and excellent long–term stability of the Au NPs–TiO_2/PANI electrodes were also confirmed.

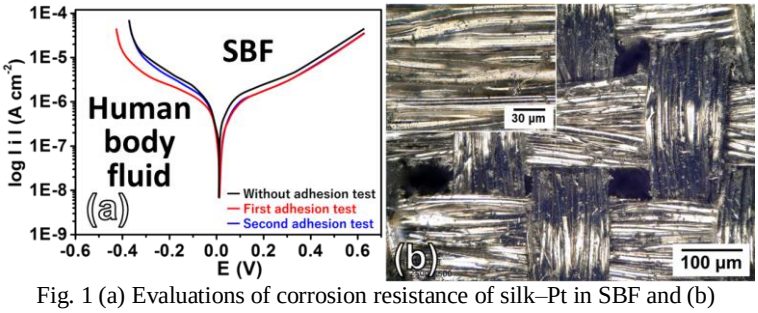

Fig. 1 (a) Evaluations of corrosion resistance of silk–Pt in SBF and (b) OM images after corrosion evaluations in SBF

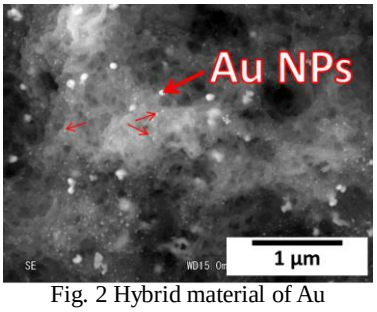

Fig. 2 Hybrid material of Au NPs–TiO_2 decorated PANI

Antibacterial activity of calcium-doped raw silk fabric

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Antibacterial materials are demanded to prevent nosocomial infections. Previously, we attempted to incorporate antibacterial activity to raw silk fabric by metal-doping (H. Chigama *et al.*, *Mater Trans*, 2019). Raw silk fabric has excellent affinity with metal ions, so metal ions can be introduced efficiently into it. Indeed, the raw silk fabric doped with calcium (R-Ca) showed strong antibacterial activity against *Escherichia coli* (*E. coli*). However, the antibacterial mechanism of R-Ca has not been clarified. In this study, we attempted to elucidate the antibacterial mechanism of R-Ca by investigating the chemical state and the dissolution behavior of doped Ca.

Commercially available raw silk fabric was soaked in a 30 mL of 1.0 M calcium chloride ($CaCl_2$) aqueous solution at 36.5 °C for 24 hours. The sample was named R-Ca. The sample surface was analyzed by an X-ray photoelectron spectroscopy (XPS). To investigate the dissolution behavior of doped Ca, R-Ca was soaked into 30 mL Tris-HCl buffer solution for 24 hours, and the Ca concentration of the solution was measured by an inductively coupled plasma optical emission spectrometer (ICP-OES). Further, to investigate the effect of Ca ions on bacterial survival, *E. coli* was incubated in phosphate buffered saline containing $CaCl_2$ at various concentrations up to 2000 mM for 1 hour. After incubation, optical density (OD) at 660 nm of the bacterial suspension was measured by ultraviolet-visible spectrophotometer. The OD corresponds to bacterial density.

From the XPS results, Ca and chlorine (Cl) were detected on the surface of R-Ca. Since the XPS spectrum did not give a peak attributed to available chlorine, it is unlikely that Cl contributed to the antibacterial activity of R-Ca, indicating that Ca was the main factor of the antibacterial activity of R-Ca. From the results of ICP-OES, Ca ion concentration was estimated to be 241 mM in the bacterial suspension during the antibacterial test. However, as shown in Fig. 1, Ca greatly inhibited the proliferation of *E. coli* at 2000 mM, but rather enhanced it up to 500 mM. Therefore, it is difficult to explain the antibacterial activity of R-Ca only by the Ca concentration. However, the released Ca ions could combine with free water that bacteria utilize for their survival and decrease the amount of free water in the suspension, and consequently induce bacterial death.

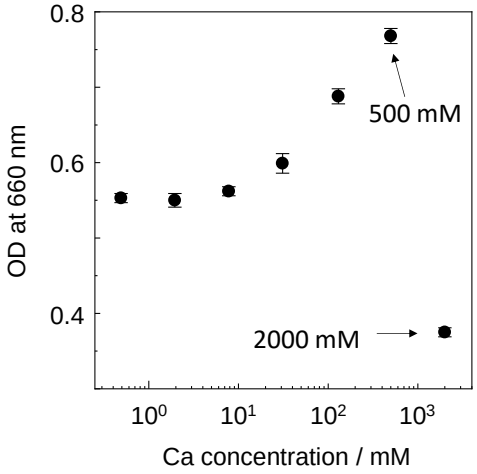

Fig. 1 OD of bacterial suspension containing Ca at various concentrations.

Session VI

Bioengineering

Gallic-acids Loaded PLGA Coating on Biodegradable ZK60

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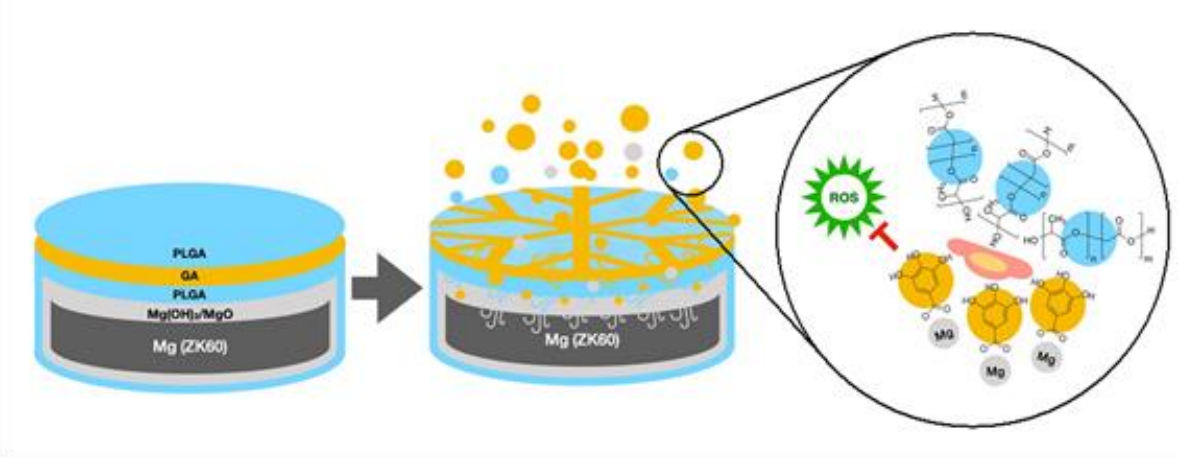
Absorbable magnesium stents become an alternative solution to treat the myocardial perfusion owing to better mechanical properties than bioabsorbable polymeric stents. However, Mg alloy without modification cannot provide the proper degradation rate to match the speed of vascular reform. A proper endothelialization covers the scaffolding region and induces regeneration after surgery. Gallic acids (GA) is a phenolic acid with attractive biological functions of anti-inflammation, improving endothelial cell's adhesion, and inhibiting smooth muscle cell proliferation. However, the direct exposure of high concentrated GA can cause cell apoptosis due to its high antioxidant activity. Thus, a small-molecule eluting coating (PLGA(GA)) is designed using a sandwich-like configuration with a GA layer enclosed between two poly-D, L-lactide-co-glycolide (PLGA) layers, which increases the corrosion resistance of magnesium alloys and prevents burst release of GA. In the electrochemical analysis, PLGA(GA) sandwich coating enhances the 2000 times corrosion resistance (in current density ($\mu A/cm^2$)) of ZK60 Mg alloy. The released GA molecules from the PLGA(GA) coating inhibit oxidation by capturing free radicals, and selectively promotes the proliferation of endothelial cells and inhibits smooth muscle cell growth. In cell migration assay, PLGA(GA) delayed wound closure in smooth muscle cell while showed potential migration ability in endothelial cell. PLGA(GA) sandwich coating not only improves the corrosion resistance of magnesium alloy but also benefit endothelization, which has great potential to prevent late-stent restenosis for developing functional vascular stents.



A Hybrid Optical / Photoacoustic Microscopic System with Novel Deconvolution Processing for Morphological and Functional Cellular Imaging

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1. Introduction

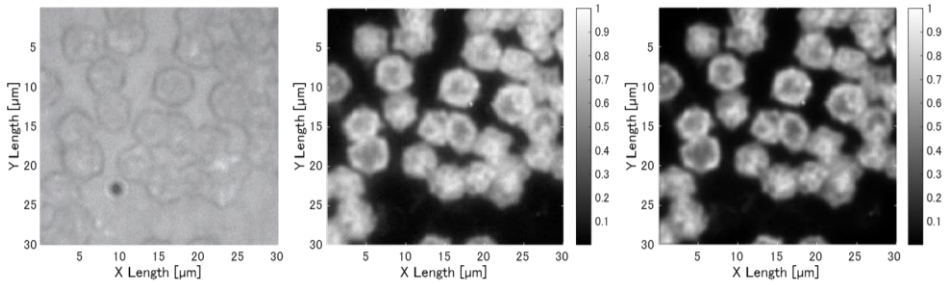
Photo-Acoustic Imaging (PAI) measures thermoelastic waves (PA waves) generated from optical absorbers inside tissues induced by pulsed laser, and is recently attracted attention as a new medical imaging modality. Optical Resolution Photo-Acoustic Microscopy (OR-PAM) is a promising PAI tool that can achieve high spatial resolution of optical diffraction limit, and visualize the absorber distribution at the single cell level. Thus, it can characterize precise cell dynamics. However, visualization of such intracellular microenvironments may require breaking through the diffraction-limited lateral resolution of OR-PAM, which may be achieved by deconvolution. Also, because the PA signal images only the optical absorber distribution, it lacks the cell morphology information, which usually acquired by optical microscopy, impeding the biological interpretation of the acquired PA properties. In this research, we develop Optical / PA hybrid microscopy that combines novel deconvolution method for detailed investigation of the intracellular microenvironment.

2. System Setup and Experiments

OR-PAM was consisted of pulsed laser (532 nm, 6 ns, 10 kHz) and objective lens (50x, NA=0.42) for irradiation, 50 MHz ultrasound transducer, 25 dB amplifier, 5 GS/s digitizer and piezo stage for PA signal acquisition. Also, optical imaging modality was devised coaxially with OR-PAM, which mainly consists of a CMOS camera and a white light source. In deconvolution processing, system's point spread function (PSF) was estimated by the 2D cross-spectral method with the theoretical model of the USAF1951 test target and the PA image, and then, the resulting PSF was deconvolved with the PA image. To test the system performance, horse red blood cells (H-RBCs) was imaged.

3. Results and Discussion

Figure (a-c) shows the result of H-RBCs imaging. The optical image can visualize the outline of RBCs, and the PA image visualized the biconcave shape particular to RBCs. In addition, the deconvolution PA image visualized the internal shape more clearly. This result shows that developed system has a potential for intracellular investigation.



(a) Optical Image (b) PA Image (b) Deconvolution PA Image

Figure. Imaging Result of Horse Red Blood Cells (H-RBCs)

Development of strong and ductile high entropy alloys for biomedical applications

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High entropy alloys (HEAs) have attracted extensive academic interests. Recently, twinning induced plasticity and transformation induced plasticity assisted dual phase non-equiatomic Fe-rich HEAs were developed, which exhibit high tensile strengths and large elongations that overcome the strength-ductility trade-off. The low SFE of the alloys are gained from tuning the chemical compositions and concentrations. On the other hand, Co-based superalloys have been widely used in manufacturing vanes and metallic orthopedic implants, owing to the superior mechanical properties and corrosion resistance. In present study, we designed novel Co-rich HEAs with manipulated mechanical properties by lowering the SFE and phase stability, achieved by adjusting the elemental concentrations of the equiatomic CoCrFeNi alloy.

The alloys were produced by arc melting in a water-cooled copper hearth, followed by homogenization, hot/cold processing, and heat treatment to control microstructures. Then, mechanical properties were measured by tensile tests at room temperature. The microstructures of the specimens were observed by scanning electron microscope (SEM) equipped with an electron backscatter diffraction detector (EBSD), and scanning transmission electron microscope (STEM) with operation voltage of 200 kV. The phase identification was carried out by X-ray diffraction (XRD).

We sucessed in demonstrating the principles for regulating SFE with assistance of *ab initio* and thermodynamic calculations [1-3]. The decrease of Mn, Ni, Fe meanwhile increase of Co, Cr concentrations does reduce fcc phase stability and the SFE of CoCrFeMnNi and/or CoCrFeNi alloys [1-2]. Moreover, the increase of Co or minor addition of Mo promotes the yield strength [3]. Based on the findings, we developed a series of strong and ductile metastable fcc-phase HEAs with mechanical properties superior to conventional biomaterials. The investigation revealed that the enhancement of mechanical properties was due to the planar behavior of dislocations, twinning induced plasticity, martensitic transformation, and Mo-addtion induced strengthening, respectively. The present study offers a guideline for designing novel alloys.

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Lymph node metastasis mouse model and its treatment

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Lymph node metastasis is a tumor cell dissemination phenomenon from a primary tumor via a lymphatic vessel to the distant organs. The study of lymph node metastasis (LNM) had some limitations, such as difficulty to design *in vitro* and a lack of suitable animal models. We created a lymph node metastasis mouse model by injecting tumor cells into the subiliac lymph node (SiLN) to metastasize in the proper axillary lymph node (PALN) of MXH10/Mo/lpr mice that have swollen lymph nodes (LNs) from 3 months of age, which is the same size as humans. Using the unique mouse model, we have proposed a lymph node-mediated hematogenous metastasis theory that cancer cells spread through veins on the surface of the sentinel LNs (SLNs) to distant organs, thus, being the origin of distant metastasis. Removal of single- or multi-LNs is the first choice for diagnosing or treating tumor susceptible LN (clinical negative lymph node, cN0LN) at pre-and intra-operative. Treatment choices will depend on the status of the LNs, especially cN0-LNs. Only about ten percent of systemically administrated anticancer drugs are retained in the lymphatic system. Therefore, lymph node metastasis targeted special treatment has not been developed yet. Here we show the effect of lymph node resection using a lymph node metastasis mouse model. As mentioned, tumor cells were injected SiLN, and tumor-bearing and tumor-free SiLNs were resected with different time intervals. We found that the removal of tumor-bearing SiLN will activate the tumor cells in the distant organs. Interestingly, removal of tumor-free SiLN induced the same activation of the tumor cells in the distant organs. Once the LN's removal induces distant metastasis, it is better to find another treatment method independent of systemic administration. We focused on delivering anticancer agents using the lymphatic network. We named it a lymphatic drug delivery system (LDDS) for preventing or limiting tumor cell spread through lymph node-mediated hematogenous metastasis route using direct injection of anticancer drugs into the tumor-bearing lymph node. By using LDDS, it is possible to treat the tumor cells in the SiLN and could control tumor cell flow in its downstream PALN. We anticipate that delivery of anticancer drugs by the LDDS will significantly benefit in the prevention and treatment of cancer metastasis using the lymphatic network.

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