Hiroshima University Research and Technology Guide

2012 Version

Creating Innovation

HIROSHIMA UNIVERSITY

Contents

Life Science

I

Life Science

Life Science

Development of Treatment Strategy for Hepatocellular Carcinoma to Improve the Long Term Prognosis

Keywords Hepatocellular Carcinoma, Prognosis, Multidisciplinary Treatment, Chemotherapy, Chronic Liver Disorder

Hiroshi AIKATA

Department Hiroshima University Hospital
Title Associate Professor / Lecturer

E-mail aikata@hiroshima-u.ac.jp
Field Gastroenterology, Hepatology

Outline

1. Background

Hepatocellular carcinoma (HCC) is one of major malignancies in Japan. It is necessary to develop and practice diagnosis and treatment strategy for improvement of long term prognosis.

2. Research Summary

To improve the prognosis of HCC patients, multidisciplinary treatment including medical, surgical and IVR approach has been performed. Especially, for advanced HCC, based on analysis of clinical outcome and prognostic factors in hepatic arterial infusion chemotherapy (HAIC) or molecular targeting therapy, new treatment strategy has been tried to be established.

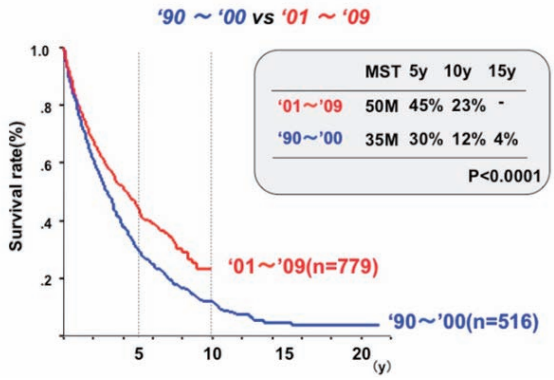
3. Result

Above multidisciplinary treatment for HCC resulted in improvement of overall survival in HCC patients (MST: 50m in '01-'09 vs 35m in '90-'00). Responder for HAIC had better survival than non-responder significantly.

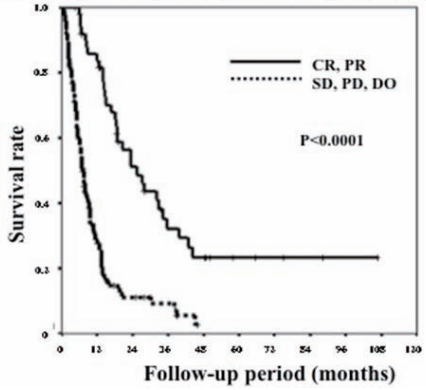
4. For Application :

It is possible to develop treatment strategy according to the characteristics of chemotherapy and molecular targeting therapy for HCC.

Overall survival rate of Hepatocellular carcinoma (n=1295)



Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma according to response (Child Pugh score 5/6 case)



Competitive Advantages

These treatment will contribute to improve the prognosis of HCC patients, in addition, to establish the clinical trial, such as randomized controlled trial as HAIC and molecular targeting therapy.

Patent/Journal/Award

Oncology., J Gastroenterol., Cardiovasc Intervent Radiol., Liver Int., J Gastroenterol Hepatol. etc.

URL http://home.hiroshima-u.ac.jp/naika1/

Life Science

Development of Revolutional Apatite-implant Complex with Simultaneous Bone Augmentation and Osseointegration

Keywords Oral Implant, QOL of Elderly Person

Yasumasa AKAGAWA

Department Institute of Biomedical & Health Sciences

Title Professor

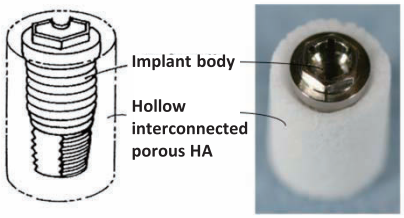
E-mail akagawa@hiroshima-u.ac.jp

Field Prosthetic Dentistry

Outline

1. Background

Loss of teeth and dentition will considerably deteriorate mastication functionality. In order to recover functionality, high level of prosthetic dentistry treatment is desired, thus implants are attracting great attention.



Invented interconnected porous HA - implant complex (Patent no. 4215595)

2. Research Summary

Successful implant treatments require sufficient quantity and quality of jawbone where implants are placed, but in reality, many patients have insufficient amount of bone in the area of missing teeth. Own bone or artificial bone is used as a solution although prognosis is not satisfactory. The present method of revolutionary implant was invented to enable osseointegration of implant and bone augmentation to take place at the same time (Pat no.4215595). Pre-clinical study has been under way on material and animals for practical application.

3. Result

Titanium implant - interconnected porous hydroxyapatite (HA) complex was prepared ex vivo, and placed into tibia or jawbone of large dogs after verification of material strength, in order to examine the degree of osseointegration biomecanically and histologically. Compared with controlled normal titanium implant, there is no significant difference in Osstell value of implant complex. Osseointegration level was sufficient, and enough bone regeneration was observed in porous material of the complex.

4. For Application

Pre-clinical study will be complete by examining the changes in osseointegration level with loaded implant. Pharmaceutical application will be made after clinical trial.

Competitive Advantages

Revolutionary development in implant treatment which allows implant placement and bone augmentation at the same time, safely and securely, which can solve existing issue of bone augmentation by only one operation.

Patent/Journal/Award

Japanese Patent No. 4215595

Paper: Initial Bone Regeneration Around Fenestrated Implants in Beagle Dogs Using Basic Fibroblast Growth Factor-Gelatin Hydrogel Complex with Varying Biodegradation Rates

Journal of Prosthodontic Research., 53: 41–47, 2009

Award: Japan Prosthodontic Society Award (2010)

URL

Life Science

How Do Patients with Alzheimer's Disease Experience Memory Impairments?

Keywords Dementia, Patients with Alzheimer's Disease, Coping Style

Sawako ARAI

Department Graduate School of Education
Title Assistant Professor

E-mail sawasawa@hiroshima-u.ac.jp Field Clinical Psychology

Outline

1. Background

In recent years, patients diagnosed with early stage of Alzheimer's disease is increasing.
And, some patient suffer from disclosure of the diagnosis .

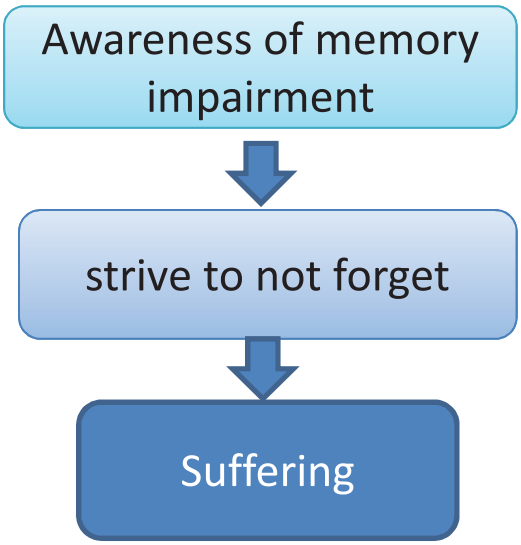
2. Research Summary

How patients with Alzheimer's disease experience the memory impairment and the disease was investigated.

3. Result

Nearly all the patients demonstrated some awareness of memory difficulties, but there were individual variations in the level of suffering. Suffering was related to their way of handling the disease. Especially, patients who strive not to forget, had been suffering.

Result



4. For Application

It became clear that some patients with Alzheimer's disease need psychological support.

Competitive Advantages

It became clear that patients' efforts to memorize afflicted the patients. The results provide interesting suggestions for counseling.

Patent/Journal/Award

URL

Life Science

Development of New Therapies for Chronic Viral Hepatitis Using Human Hepatocyte Chimeric Mice

Keywords Human Hepatocyte Chimeric Mice, Hepatitis Viruses

Kazuaki CHAYAMA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail chayama@hiroshima-u.ac.jp

Field Internal Medicine, Gastroenterology

Outline

1. Background

Human hepatocyte chimeric mice are developed by engrafting human hepatocyte into Alb-uPA/SCID mice (PhoenixBio Co., Ltd., Higashi-Hiroshima, Japan). The mice are shown to be susceptible to human hepatitis viruses infection such as hepatitis B (HBV) or hepatitis C virus (HCV), and keep the high viral titer in serum for several months.

2. Research Summary

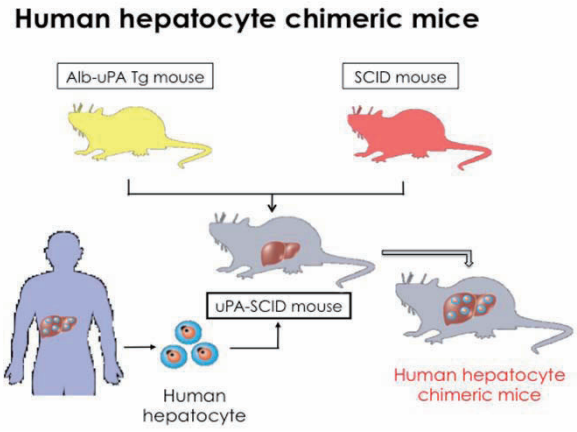
Using HBV or HCV-infected human hepatocyte chimeric mice, we investigate the anti-viral effect of new drugs, and attempt to develop new treatments for chronic viral hepatitis. Reverse-genetically engineered mutated viruses-infected mice are useful for development of new treatments for drug-resistant viruses.

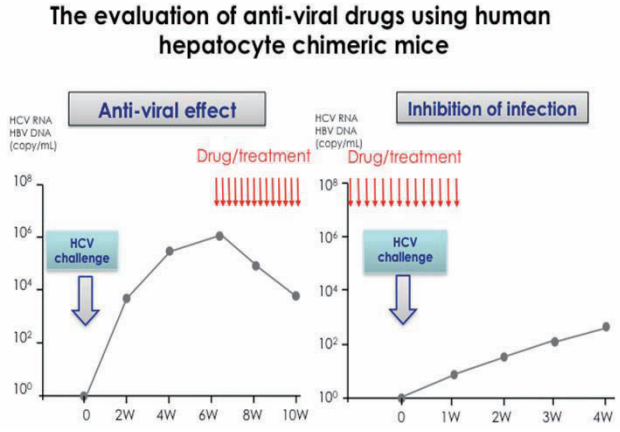
3. Result

We have found that some agents had the effect of inhibition of viral replication, inhibition of viral infection, enhancing interferon. We have developed new treatments for HCV infection, and some clinical studies are on the way.

4. For Application

We welcome cooperative investigations for hepatitis viruses with research laboratories or drug companies using human hepatocyte chimeric mice.





Competitive Advantages

Human hepatitis viruses infect only chimpanzee and human livers. The human hepatocyte chimeric mouse is the only small animal model infected with human hepatitis viruses. We have extensive experience of investigations using this animal model.

Patent/Journal/Award

Sainz B Jr, et al. ***Nat Med*** 2012; 18: 281–5, Hiraga N, et al. ***Hepatology*** 2011; 54: 764–71
Hiraga N, et al. ***Hepatology*** 2011; 54: 781–8, Saeed M, et al. ***Hepatology*** 2011; 54: 425–33
Ohara E, et al. ***J Hepatol*** 2011; 54: 872–8, Ohira M, et al. ***J Clin Invest*** 2009; 119: 3226–35
Matsumura T, et al. ***Gastroenterology*** 2009; 137: 673–81

URL http://home.hiroshima-u.ac.jp/naika1/e/

Life Science

Identification of High Risk Patients to Develop a Pulmonary Arterial Hypertension

Keywords Pulmonary Hypertension

Yoshihiro DOHI

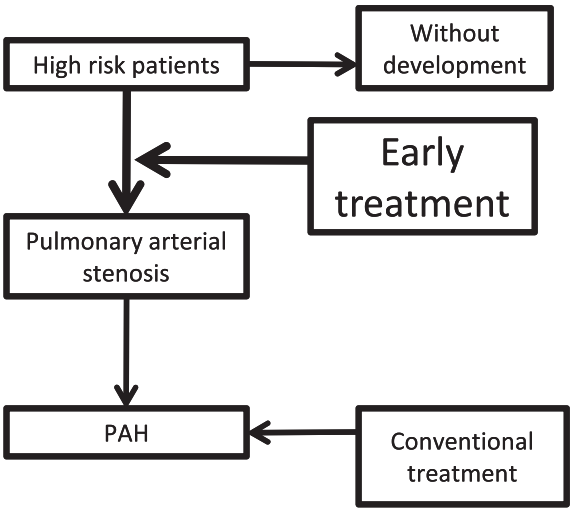
Department Hiroshima University Hospital
Title Assistant Professor
E-mail yuyudohi@gmail.com
Field Medical, Cardiovascular

Outline

1. Background

Treatment of pulmonary arterial hypertension (PAH) have been studied in patients in an advanced stage. However, even in less compromised individuals, lung lesions have already advanced.

Early diagnosis is of great importance in PAH.



2. Research Summary

This study enrolled patients with a diagnosis of connective tissue disease. To identify specific findings associated with PAH, we collects and estimates the data of pulmonary and cardiac functional tests.

3. Result

Now this study is in progress.

4. For Application

Competitive Advantages

Patent/Journal/Award

URL

Life Science

The Evaluation of the Intractable Chronic Pain in Psychosocial Factor and Specificity Symptom

Keywords Chronic Pain, Neuroimaging, Neuropathic Pain

Mitsuru DOI

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail doi326@hiroshima-u.ac.jp

Field Oral Maxillofacial Surgery, Dental Anesthesiology

Outline

1. Background

Trigeminal neuropathy following dental treatment is one of the most difficult conditions to treat. Prolonged abnormal sensation tends to be observed in cases whose nerves were moderately or severely damaged.

2. Research Summary

The purpose of this study was to guess that the severity of nerve injury could be measured with electric and tactile detection thresholds.

3. Result

Assessing not only intensity of hypoesthesia but also quality of dysesthesia is important to evaluate precise patient's sensory damage and complaint. And the electrical detective threshold higher than 2.15 mA showed a tendency of prolongation of abnormal sensation. Using quantitative sensory testings, we can roughly predict prolonged abnormal sensation in fresh cases. More study is required for brain function imaging evaluation along with the functional MRI imaging under emotion stimulation test.

4. For Application

Further research will be conducted for more reproductive and reliable prognosis based on increased size of data.

Competitive Advantages

Pain is a sensation that cannot be shared with others and the severity of pain is affected by individual cognition against pain. This research provides novelty in unique evaluation of psychosocial factors hard to quantify.

Patent/Journal/Award

URL

Life Science

A Versatile Modification of Physical Properties of Organic Materials by Introduction of Oxaalkyl Chains

Keywords Oxaalkyl Chain, Lowering Melting Point, Crystallization Inhibition

Koichi FUKUHARA

Department Graduate School of Science

Title Assistant Professor

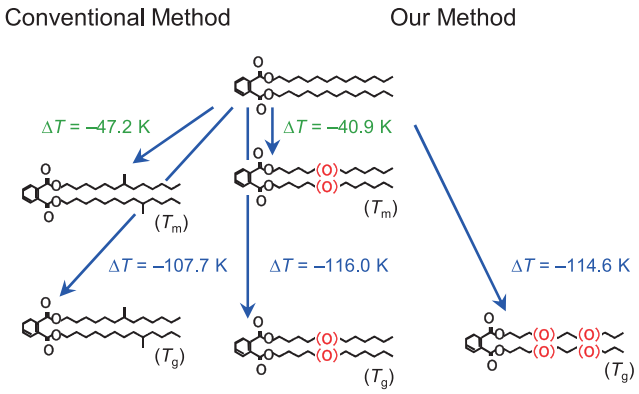
E-mail kfuku@sci.hiroshima-u.ac.jp

Field Materials Chemistry, Applied Chemistry , Physical Chemistry

Outline

1. Background

The intrinsic conformational form of the alkyl chain is a planar structure with an all-trans conformation, while that of the oxaalkyl chain is a bent structure. We have studied the molecular structures of a number of oxaalkyl compounds and identified two distinctive molecular forms in the solid state: one with an ordinary bent structure and the other with a peculiar planar structure. We have found that a self assembled planar oxaalkyl compound, which has the similar structure of alkyl compounds, shows unique physical properties such as very low melting point and crystallization inhibition.



2. Research Summary

As many kinds of organic materials have alkyl chains in the molecules, substitution and/or introduction of oxaalkyl chains in the organic molecules will add new feature to the materials. Accumulation of basic experimental data is needed because this method is based on a new intermolecular interaction theory. Systematic studies are now in progress in order to elucidate the physical properties of various functional materials.

3. Result

An application example for plasticizers is shown. Grass transition temperature (T_g) of the plasticizer modified by our method (subsutitution of the oxaalkyl chain to alkyl chain) is lower than that of the plasticizer modified by the conventional method (branching of alkyl chain). Valuable experimental results have also been obtained for other materials, such as surfactants and polymers.

4. For Application

Development of new functional materials will be expected by applying our method.

Competitive Advantages

Promising new features are: (1) applicable to many organic materials (high versatility); (2) based on a new intermolecular interaction theory (possibility of development of new organic materials); (3) unnecessity of any special ingredients or synthetic methods (low-cost and low-risk); (4) simple molecular structure (easy molecular design); (5) concomitance to conventional method (high compatibility to other methods), etc.

Patent/Journal/Award

Japanese Patent Unexamined Publication No. 2008–031149

URL

Life Science

Activin A Induces Craniofacial Tissue from Undifferentiated *Xenopus* Ectoderm *in vitro*

Keywords Tooth Induction, Jaw Induction, Activin A

Yasuto FUKUI

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

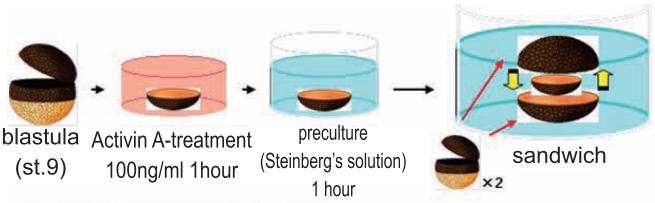
E-mail yfu@hiroshima-u.ac.jp

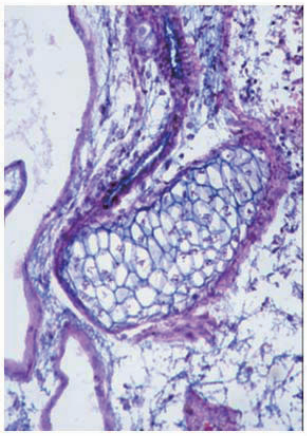
Field Dentistry, Dental Surgery

Outline

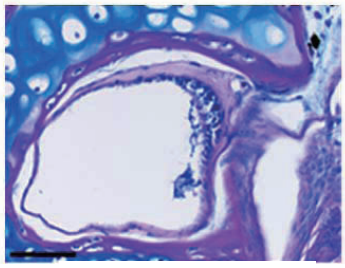
1. Background

Activin A has potent mesoderm-inducing activity in amphibian embryos and induces various mesodermal tissue *in vitro* from the isolated presumptive ectoderm. At low concentrations of activin A, ventral mesoderm, such as blood-like cells, coelomic epithelium, and mesenchyme are induced. At intermediate concentrations, muscle and neural tissues are induced. At high concentrations, notochord is induced. The sandwich culture method demonstrates that activin-treated presumptive ectoderm can function as a head or trunk-tail organizer, depending on the activin A concentration and preculture period after the activin treatment.





Indeced craniofacial tissue



Tooth germ-like tissue

2. Research Summary

This study demonstrates that craniofacial tissue can be induced by using the sandwich culture *in vitro* and examines whether the induced tissue has the position information on the head using head specific marker. Furthermore, the induced tissue which has head position information is transplanted to *Xenopus* laevis embryos and cultured for a long period of time, and the induced tissue is studied.

3. Result

In this study I can induce the tissue which has the position information on the head using the sandwich culture. And transplanted tissue to *Xenopus* laevis induced tooth germ-like tissue by long term culture.

4. For Application

This method will be able to become a new technique of tissue engineering if the Xenopus sandwich culture can be transposed to mammalian ES cell or iPS cell.

Competitive Advantages

This method can induce many tissues in serum free condition and can induce as organs.

Patent/Journal/Award

Proc Natl Acad Sci U S A. 2002 Nov 26; 99 (24): 15474–9. Epub 2002 Nov 7.

Dev Growth Differ. 2003 Oct-Dec; 45 (5–6): 499–506

Int J Dev Biol. 2004 Dec; 48 (10): 1105–12

URL

Life Science

Functional Analysis of Signal Complexes Containing Insulin Receptor Substrates (IRSs)

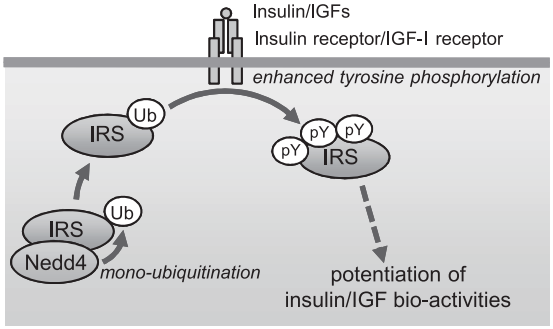
Keywords Insulin, IGF, Metabolic Syndrome, Diabetes, Cancer

Toshiaki FUKUSHIMA
Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail Tofu@hiroshima-u.ac.jp
Field Biomedical Science, Metabolism, Endocrinology, Molecular Biology

Outline

1. Background

Insulin and insulin-like growth factors (IGFs) play important roles in the regulation of carbohydrate/lipid metabolism and somatic growth. Their binding to the specific receptors activates receptor-intrinsic tyrosine kinases, followed by tyrosine phosphorylation of the substrates including IRSs. Stimulation of target cells with various hormones, cytokines and nutritional factors often suppresses tyrosine phosphorylation of IRSs, which causes insulin resistance and subsequent metabolic syndrome. In contrast, aberrantly intense tyrosine phosphorylation of IRSs often promote cancer malignancy. However, molecular mechanisms under the regulation of tyrosine phosphorylation of IRSs remain unclear.



Our findings:
a novel regulation of insulin/IGFs bio-activities
by IRSs-associated proteins

2. Research Summary

We had found that IRSs form high-molecular-mass complexes containing various proteins, and that the complexes can modulate insluin/IGFs signals and bioactivities. Thus, we identified components of the complexes and analyzed their functions.

3. Result

We identified E3 ubiquitin ligase Nedd4 as one of IRS-associated proteins. Mono-ubiquitination of IRSs by Nedd4 causes the recruitment of IRSs to plasma membrane, which leads increases in their availability to receptor tyrosine kinases and the augmentation of insulin/IGFs signals. These findings raised the possibility that changes of the interaction of Nedd4 with IRSs or Nedd4 activity might be related to pathology of insulin resistance and cancer malignancy. Analyses of other IRSs-associated proteins are in progression.

4. For Application

We expect to collaborate to screening chemical compounds targeting to IRSs-associate proteins with pharmaceutical companies. If we can manipulate their molecular functions using compounds, it will enable fine-tuning of insulin/IGFs activities. This study will contribute to the development of a novel therapeutic approach toward metabolic syndrome and cancer.

Competitive Advantages

Although thiazolidine derivatives and biguanides are widely used as insulin sensitizer, their mechanisms of action remain unclear. We propose IRSs-associate proteins as novel candidates of molecular targets in metabolic syndrome and cancer therapeutics. Drugs targeting of IRSs-associated proteins can modulate insulin/IGF activities with high specificity, and this specific mechanisms of action will offer advantages over other existing drugs.

Patent/Journal/Award

Mol Cell Endocrinol. 2011 Sep 15; 344 (1–2): 81–9, Biochem Biophys Res Commun. 2011 Jan 21; 404 (3): 767–73, The best presentation award in Gordon Research Conference: Insulin like growth factors in physiology and disease, Ventura, CA, 2011.2.

URL http://home.hiroshima-u.ac.jp/ikagaku/

Life Science

Changes in Interhemispheric Inhibition from the Active to Resting Primary Motor Cortex during a Fine-motor Manipulation Task

Keywords Fine-motor Manipulation Task, Ipsilateral Primary Motor Cortex Excitability, Interhemispheric Inhibition, TMS

Kozo FUNASE

Department Graduate School of Integrated Arts and Sciences

Title Professor

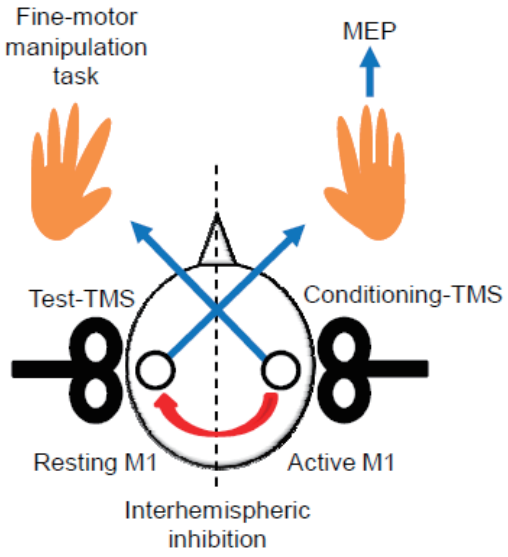
E-mail funase@hiroshima-u.ac.jp

Field Human Motor Control, Neuro-rehabilitation

Outline

1. Background

A number of TMS studies have suggested that the activation of the ipsilateral primary motor cortex (M1) during the performance of a unilateral hand motor task is mediated by transcallosal pathways. However, the effects of performing a sensorimotor task on interhemispheric neural mechanisms have not been examined in detail. We examined the changes in interhemispheric inhibition (IHI) from the active to the resting M1 during the performance of a fine-motor manipulating task and compared them with those produced during a simple voluntary contraction task.



2. Research Summary

The effect of performing a fine-motor manipulation task as a sensorimotor task on the IHI induced from the active M1 to the resting M1 was examined in ten right-handed subjects , assessed by motor evoked potentials (MEP) evoked by transcranial magnetic stimulation (TMS) . As a result, a marked facilitation of the ipsilateral M1 excitability was observed during performing a fine-motor manipulation task than a simple finger muscle contraction.

3. Result

The present findings suggest that the increased IHI from the active to the resting M1 observed during a fine-motor manipulation task was linked to reductions in the activity of the ipsilateral intracortical inhibitory circuit, as we reported previously.

4. For Application

In order to verify the actual effect of a fine-motor manipulating task performed by a healthy hand of hemiplegic patient, collaboration with the rehabilitation facility will be useful.

Competitive Advantages

An actual daily motor task using chopsticks as a sensorimotor task is adopted in the present study. This fine-motor manipulation using chopsticks induces the marked facilitation of ipilateral M1 excitability innervating the contralateral hand muscle.

Patent/Journal/Award

Changes in interhemispheric inhibition from the active to resting primary motor cortex during a fine-motor manipulation task. Morishita T, Uehara K, Funase K, Journal of Neurophysiology, in press, doi:10.1152/jn.00888.2011

Increased excitability and reduced intracortical inhibition in the ipsilateral primary motor cortex during a fine-motor manipulation task. Morishita T, Ninomiya M, Uehara K, Funase K, Brain Research, 1371: 65–73, 2011

URL http://home.hiroshima-u.ac.jp/funase/index1.htm

Life Science

Creation of High Performance Host Yeast for the Production of Human-type Sphingolipids

Keywords Sphingolipid, Ceramide, Yeast, Genetic Recombination, Skin, Barrier, Moisture

Koichi FUNATO

Department Graduate School of Biosphere Science

Title Associate Professor

E-mail kfunato@hiroshima-u.ac.jp

Field Agricultural Chemistry, Boundary Agriculture, Internal Clinical Medicine

Outline

1. Background

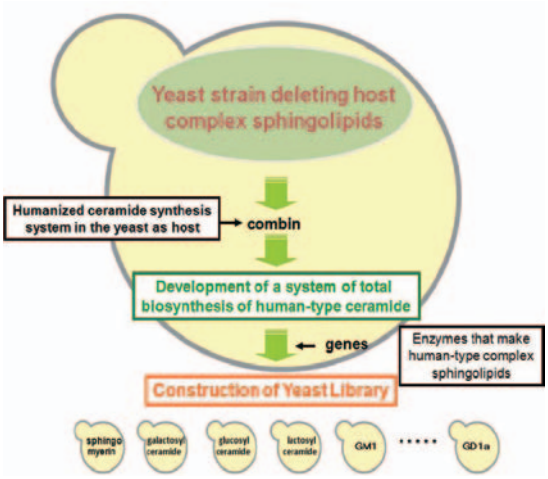
Ceramide is lately the object of attention as a material for therapeutic drug or cosmetics/health food in treating dermatosis accompanying dry/sensitive skin. So far, animal derived materials such as from cows have been used as raw material for ceramide, but because of concern of infectious diseases, plant derived ceramides such as from rice, wheat, beans and potatoes are now the mainstream. However, since plant derived ceramides are different from human-type ceramides and have low productivity, there is a strong desire for the development of new production technology that can overcome these problems.

2. Research Summary

Budding yeast has been widely used in the fields of cosmetics, health food and medicine industry as a host for the production of useful substances. We started to develop the yeast that produces a human-type ceramide using genetic recombination.

3. Result

By changing and controlling the biosynthesis and metabolism system of sphingolipids of budding yeast, introducing the necessary human gene and controlling localization of gene product, we succeeded in developing a system that effectively produces a human-type ceramide in the yeast.



Future developments and industrial use

Development 1	Development of a system of total biosynthesis of human-type ceramide
Industrial use	Supply of cheap high performance ceramide -upgrading existing industry/higher added value -contribution to market development of ceramide as material for health and beauty
Development 2	Construction of yeast library of human-type sphingolipids
Industrial use	Supply of human-type sphingolipids as functional materials. -Use as model system for animals, and use for screening of novel drugs and production of lipid antibodies. -Application for development of new clinical examination methods.

4. For Application

A serious issue of the current system is that a part of the humanized ceramide is converted into a hybrid through complex sphingolipid synthetic pathway of the host yeast. To solve the issue of this hybrid, it is unavoidable to establish a strain that deletes complex sphingolipid synthetic pathway of the yeast completely.

Competitive Advantages

We developed first in the world the production system of human ceramide (ceramide NS) within the yeast. If a strain can be constructed that can grow and delete complex sphingolipids, market can be supplied with highly production effective and thus cheap humanized sphingolipids and the yeast library by introducing a humanized ceramide synthesis system to that strain, and it will greatly contribute to the development of the sphingolipid industry.

Patent/Journal/Award

Japanese Patent No. 4737531, International Application PCT/JP2008/059241, International Application PCT/JP2008/05548

URL

Life Science

Development of New Technologies for the Medicine Using the Chicken Antibodies

Keywords Chicken Monoclonal Antibodies, Diagnostic Reagent, Humanized Antibodies, Therapeutic Antibody

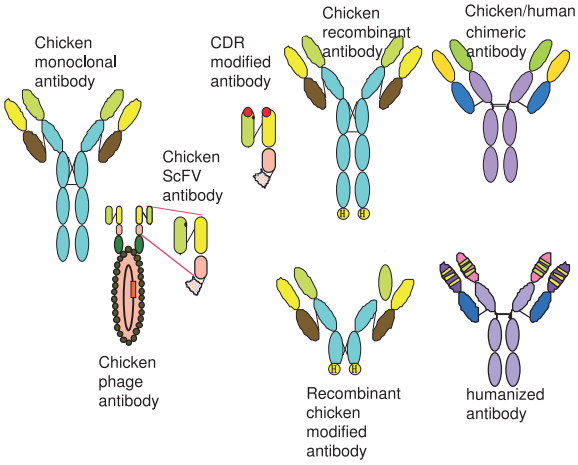
Shuichi FURUSAWA
Department Graduate School of Biosphere Science
Title Professor
E-mail sfurusa@hiroshima-u.ac.jp
Field Applied Veterinary Sciences, Basic Veterinary Sciences

Outline

1. Background

It has been already generalized it to make mouse monoclonal antibody. However, many antigens that antibody titer did not go up even if we immunised it to a mouse existed, and Armenian hamster came to be used as an immunity animal.
Gene library of the antigen binding site of the antibody as a useless case. However, these all has a fault and do not reach a decisive method out of the situation.
It was hard to make it with the mammals and an antibody with high affinity to the antigen of the antibody came to be provided by immunising an antigen to the birds which were not mammalian by using the chicken fusion cell which we made for the first time in the world.

These antibodies are available in our laboratory



2. Research Summary

There is antibody making falling into the difficult situation for making in various companies. We develop a technique to make recombinant antibody protein, chimeric antibody, and humanized antibody. Moreover, we develop those in large quantities using molecular biological techniques.
And we study the development such as the new making methods.

3. Result

We succeed in a chicken-type, humanized-type antibody that a company pro-various medical care demands by the method that we build it, and performed patent application.
In addition, we give fundamental experiment data for the practical use as various inspection reagents and pharmaceutical products.

4. For Application

The assumption industry is a company of pharmaceutical products, but there are various types of industry with the applied aspect as well as it.

Competitive Advantages

The antibody making using birds (chicken cell line and an ostrich) unlike mammals comes into the limelight as influenza measures masks as well as the antibody industry.
However, only our group can develop cheap and large quantities high affinity antibody.

Patent/Journal/Award

Chicken monoclonal antibody produced by a production method of the cock type monoclonal antibody and the production method concerned, Japanese Patent No. 4273230 (+ other 4 Patents.)

URL http://www.hiroshima-bm.com/

Life Science

Participation of Plasminogen Activator/Plasmin System in Cell-cell Adhesion and Invasive Growth of Oral Squamous Cell Carcinoma Cells

Keywords Plasminogen Activator/Plasmin System, E-cadherin, α_2-antiplasmin

Tomoaki HAMANA

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

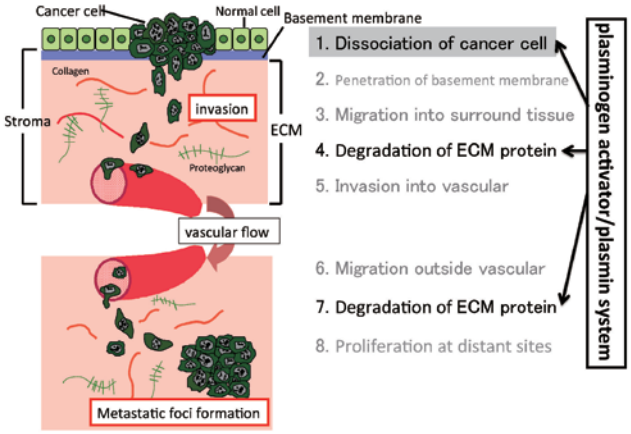
E-mail tomoh57@hiroshima-u.ac.jp

Field Surgical Dentology

Outline

1. Background

The proteolytic activity and migration of cancer cells closely participate with tumor invasion and metastasis. It is well known that the plasmin plays a main role in extracellular matrix (ECM) proteases, and regulates tumor invasion and metastasis. In addition, it is indicated that the plasmin regulates the proteolytic processing and affects the expression and function of cell membrane proteins. However, it isn't being cleared a role of plasminogen activator/plasmin system in the fragmentation, expression and function of E-cadherin which regulates cell-cell adhesion. I thought that if the plasmin suppresses the function of E-cadherin, impairs the intercellular adhesion and facilitates the cell migration of squamous cell carcinoma (SCC) cells. Therefore, it was suggested that the inhibition of plasmin activity not only suppresses the proteolytic activity but reduces the migration of cancer cells, and suppresses tumor invasion and metastasis.



Role of plasminogen activator/plasmin system in invasion and metastasis

2. Research Summary

The influence of plasminogen activator/plasmin system in the proteolytic processing, expression and function of E-cadherin on oral SCC cells was investigated. Moreover, it was examined whether the induction of α_2-antiplasmin (α_2-AP) which is the plasmin inhibitor affects expression of E-cadherin and the cell aggregation and invasive growth of oral SCC cells.

3. Result

The plasmin cleaved the ectodomain of E-cadherin and reduced the cell aggregation and promotes the cell migration by downregulation of E-cadherin-mediated cell-cell adhesion in SCC cells. It was indicated that the induction of α_2-AP suppressed E-cadherin processing by inhibit plasmin activity, and reduced the cell migration and invasive growth of SCC cells.

4.For Application

In vivo studies will be required to establish the safe and effective α_2-AP protein expression system with simple injection of the α_2-AP gene into oral SCC tissue.

Competitive Advantages

It isn't being cleared a role of plasminogen activator/plasmin system in the processing, expression and function of E-cadherin on SCC cells. The downregulation of the plasminogen activator/plasmin system by α_2-AP might be a potent therapeutic approach to prevent the progression of oral SCC.

Patent/Journal/Award

International Journal of Oncology 27: 693–698, 2005.
Oncology Reports 17: 417–423, 2007

URL

Life Science

Study on Activation of Salivary Secretory Function with Salivary Gland Massage

Keywords Salivary Gland Massage, Saliva Secretion, Dry Mouth

Kumiko HARA

Department Institute of Biomedical & Health Sciences

Title Associate Professor / Lecturer

E-mail khara@hiroshima-u.ac.jp

Field Odontology

Outline

1. Background

Facial and body massage has beneficial effects on relieving stress and pain. However, massage therapy may be dependent on the mental state of the subject, raising a complicated problem regarding its effectiveness. Facial massage around the area of the salivary glands, termed salivary gland massage, enhances saliva secretion . However, the factors responsible for stimulating saliva secretion on salivary gland massage remain obscure.

2. Research Summary

Subjects: young women (n=46; aged 20.5 ± 0.3 yr)
elder subjects (n=13; aged 81.5 ± 4.1 yr)

We measured the saliva secretion rate on self-massage and assisted massage in young and elder subjects.

For assessing the long-term effects of salivary gland massage, we checked the saliva secretion rate and the feeling of oral dryness in the elder subjects 6 months later.

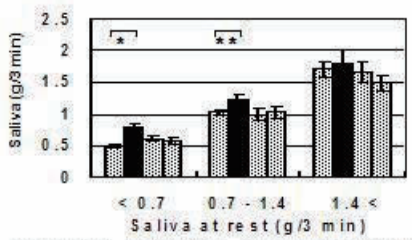
3. Result

Self-massage significantly increased the saliva secretion rate in the young and elder subjects, but assisted massage increased it only in elder subjects. Self-massage was effective especially in the subjects with lower secretion rate at rest.

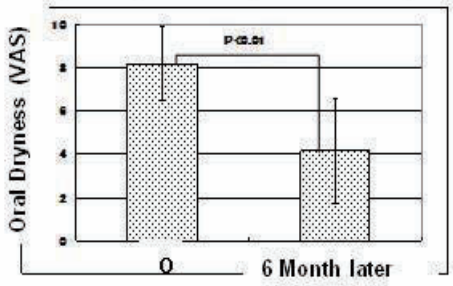
The long-term salivary gland massage improved the feeling of oral dryness.

4. For Application

Massage instrument for the salivary gland massage helps the improvement of the salivary gland function.



Increase in Saliva Secretion in Young Subjects by Salivary Gland Massage



Improvement of Oral Dryness in 5 Elder Subjects by Salivary Gland Massage

Competitive Advantages

Salivary gland hypofunction leads to severe disorders of oral function, such as disturbances in taste, mastication, swallowing and speaking. Management of dry mouth is necessary for a higher quality of life.

Patent/Journal/Award

The Journal of Hiroshima University Dental Society 40(1), 10–29, 2008.

URL

Life Science

New Defense System against Invasive Bacteria in Host Cells

Keywords Autophagy, Bacterial Infection

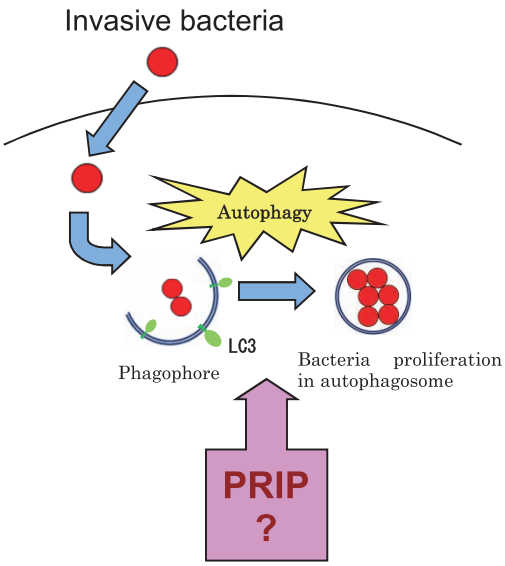
Kae HARADA

Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail kae@hiroshima-u.ac.jp
Field Pharmacology

Outline

1. Background

We previously reported that PLC-related catalytically inactive protein (PRIP) binds to GABARAP ($GABA_A$ receptor associated protein) and regulates the cell surface expression of $GABA_A$ receptors. LC3 (microtubule associated protein light chain 3), an autophagy regulating protein is a homologue of GABARAP. Therefore, we explored whether PRIP regulates autophagy system.



2. Research Summary

We focused on the selective autophagy against invasive bacteria in host cells.

3. Result

We used PRIP deficient cells and revealed a novel regulating system of the bacterial proliferation which is modulated by selective autophagy in host cells.

4. For Application

We purpose the development of new drugs for invasive bacteria in human. We are going to progress the study by using experimental animal models.

Competitive Advantages

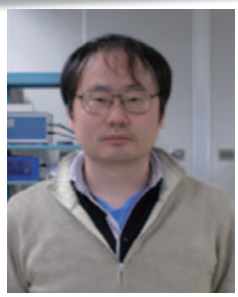
Our study is focused on the mechanism in which bacteria intracellularly survive in long period in host cells. Resulting new drugs can be more effective by the combinations with conventional antibiotics.

Patent/Journal/Award

URL

Life Science

Roles of P/Q Type Voltage-gated Calcium Channel in the Postnatal Development of Neuronal Circuits



Keywords Electrophysiology, Neuron, Development, Cerebellum

Kouichi HASHIMOTO

Department Institute of Biomedical & Health Sciences

Title Professor

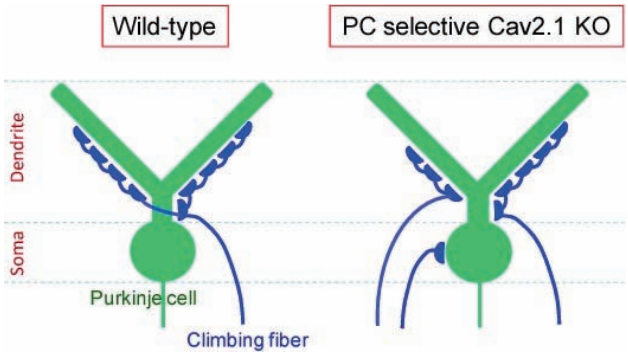
E-mail hashik@hiroshima-u.ac.jp

Field Neuroscience, Physiology

Outline

1. Background

Immature neurons initially make synaptic connections not only to their final targets but also to other neurons. During postnatal development, functionally important synapses are strengthened, and less important synapses are weakened relative to the important ones. The weakened synapses are finally eliminated morphologically.



2. Research Summary

We analyzed the roles of the P/Q type voltage-gated Ca2+ channel in postnatal refinement of neuronal circuits using the cerebellar climbing fiber (CF) to Purkinje cell (PC) synapse as a model system. At birth, each PC is innervated by multiple CFs. Then, single CF input is selected, matured and strengthened, while surplus CFs are eliminated. By the end of the third postnatal week, most PCs become innervated by single CFs. We generated the mutant mice in which P/Q channel was selectively eliminated from the PCs, and analyzed postnatal development of CFs.

3. Result

We found that selective strengthening of a single CF and the following elimination process were severely impaired in PC specific P/Q channel knockout mice.

4. For Application

This analysis might advance the understanding of the developmental disability in the future.

Competitive Advantages

The analysis of circuits development is difficult because of their complexity especially in central nervous system. We overcame this disadvantage by analyzing the cerebellar CF to PC synapse in which postnatal changes were able to be analyzed at the synaptic level.

Patent/Journal/Award

Hashimoto, K., Tsujita, M., Miyazaki, T., Kitamura, K., Yamazaki, M., Shin, HS., Watanabe, M., Sakimura, K., Kano, M. Postsynaptic P/Q-type Ca^{2+} channel in Purkinje cell mediates synaptic competition and elimination in developing cerebellum. ***Proc Natl Acad Sci U S A***. 108, 9987–9992 (2011).

URL http://home.hiroshima-u.ac.jp/physiol2/

Life Science

Development of a Variety of Analysis Softwares for Magnetoencephalography

Keywords Magnetoencephalography, MATLAB, Freeware

Akira HASHIZUME

Department Culture and Education Office

Title Part-time Lecturer

E-mail hashizume@jinyoukai.or.jp

Field

Outline

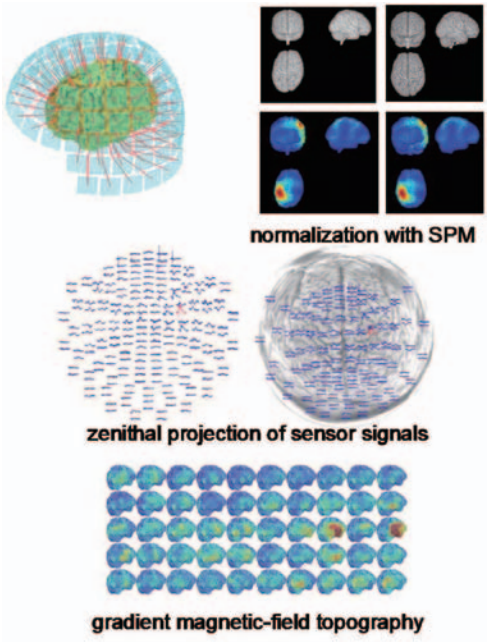
1. Background

Exsiting magnetoencephalography (MEG) softwares are not handy and we developed original softwares and released them as freewares.

2. Research Summary

We use programming language Matlab (MathWorks, USA) and developed a software deploying FIFF file, Elekta-Neuromag's MEG data file on Matlab, and made following signal processing tools, gradient magnetic-field topographny, source estimation software based on minimum-norm or minimum variance, normalization with statistic parametric mapping (SPM), projection of sensor signals over zenitial expanded brain surface images.

Some functions are built with Matlab Compiler as freeware not requiring Matlab, and released on my home page.



3. Result

My software converting FIFF file into Matlab's data file, MAT file is now widely used in Elekta-Neuromag's MEG users. Another software for epilepsy research is used in Nishi-Niigata central hospital, that reported as papers.

4. For Application

Our developed softwares are actually used and other MEG site uses them in clinical front.

Competitive Advantages

Our software is freeware, expensive Matlab, workstation, licence fees are not required.

An MEG user developed these tools and they are quite easy to handle.

Patent/Journal/Award

Hashizume A.Brain Res.1145:175–179,2007

Hashizume A,Hiroshima J.Med.Sci.59:21–5,2010

Hiroshima Journal of Medical Sciences excellent paper award 2011

URL http://meg.aalip.jp/

Life Science

Genome-wide Profiles of the Core Clock Protein BMAL1 Target by Using Multiple High-throughput Approaches

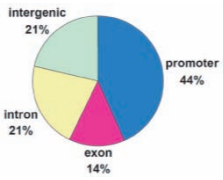
Keywords Circadian Rhythms, Transcription, Metabolism

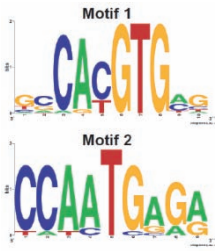
Fumiyuki HATANAKA
Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail f-hatanaka@hiroshima-u.ac.jp
Field General Medical Chemistry

Outline

1. Background

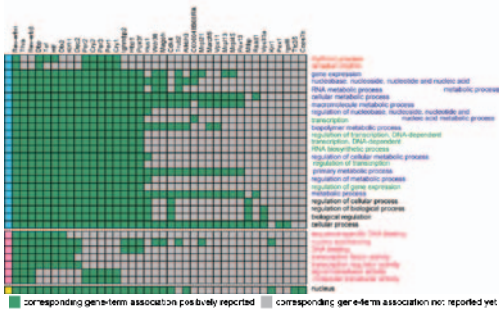
Circadian rhythms are common to most organisms and govern much of homeostasis and physiology. BMAL1 is a critical circadian transcription factor that regulates genes via E-box elements in their promoters.





2. Research Summary

Here we use multiple high-throughput approaches including chromatin immunoprecipitation (ChIP)-based systematic analyses and DNA microarrays combined with bioinformatics, to generate genome-wide profiles of BMAL1 target genes. The database generated in this study constitutes a useful resource to decipher the network of circadian gene control and its intimate links with several fundamental physiological functions.



3. Result

We reveal that, in addition to E-boxes, the CCAATG element contributes to elicit robust circadian expression. BMAL1 occupancy is found in more than 150 sites, including all known clock genes. Importantly, a significant proportion of BMAL1 targets include genes that encode central regulators of metabolic processes.

4. For Application

Understanding precise molecular mechanism of circadian rhythms, and finding out the new seeds of many disease such as a lifestyle diseases.

Competitive Advantages

Results of genome-wide profiles will provide the efficient and proper screening for new seeds.

Patent/Journal/Award

Hatanaka F. et al., Genome-wide profiling of the core clock protein BMAL1 targets reveals strict relationship with metabolism., *Mol. Cell. Biol.*, 30: 5636–48, 2010

URL http://home.hiroshima-u.ac.jp/anatomy2/index.html

Life Science

Detection Method for Epilepsy Using ^{11}C Flumazenil-PET

Keywords Epilepsy, Diagnostic Imaging, Flumazenil-PET, Compartment Analysis

Toru HIGAKI

Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail higaki@hiroshima-u.ac.jp
Field Medical Systems

Outline

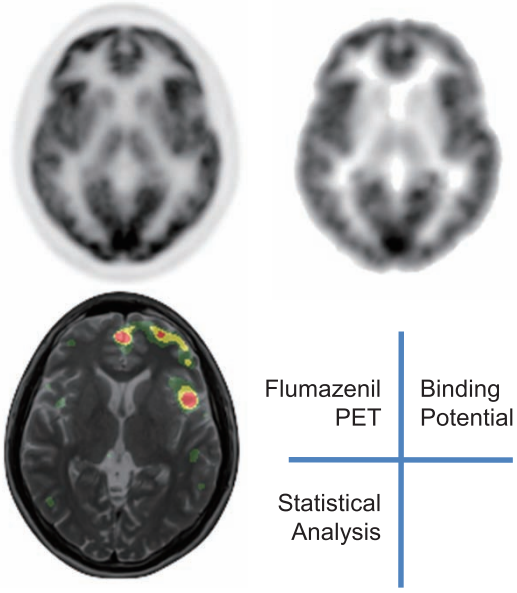
1. Background

Brain tissue at epileptic focus is known for having some anomaly. In this research, we evaluate a detectability for epileptic focus using ^{11}C-Flumazenil-PET. Flumazenil has the property of binding specifically with neuronal cells.

2. Research Summary

Ten volunteers and 5 patients were enrolled for this study. The volume data is acquired 27 times, that is 4-dimensional data, we estimate flow of the flumazenil and binding potential between the flumazenil and neurons with analyzing the 4D data by compartment analysis.

We detected epileptic focus automatically on the assumption that binding potential on epileptic focus has declined. We applied statistical analyze to detect epileptic focus using normal database.



3. Results

Our method could identify obscure lesions which could not be detected by MRI and FDG-PET.

4. For Application

After preliminary clinical trials, we will introduce our method to clinical sites by implementation on workstation for medical image analysis.

Competitive Advantages

Our new detection method for epileptic focus has possibility to find diseases that are not found by any other imaging modalities such as MRI and FDG-PET.

Patent/Journal/Award

URL

Life Science

Development of the Washing-sterilizer by the Ordinary Pressure Superheated Steam Use

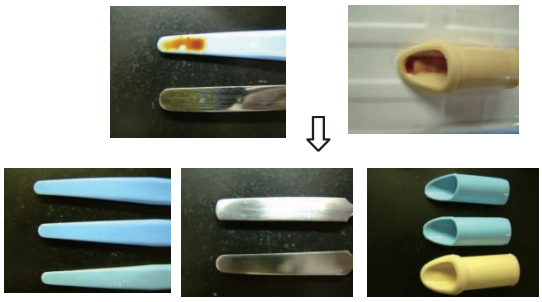
Keywords Washing, Sterilization, Medical Device, Superheated Steam, Infection Control, Standard-precaution

Takamune HINO
Department Hiroshima University Hospital
Title Associate Professor / Lecturer
E-mail thino@hiroshima-u.ac.jp Field Periodontics, Endodontics, Periodontal Medicine

Outline

1. Background

There is a duty for maximum effort to prevent the infection, while the medical side offers updated and excellent medical treatment to patients.
There is the perfection of washing, disinfection, sterilization as one of the gist of the infection control, and development and improvement of the washing-, sterilization-device based on the concept of standard-precaution have been required.



2. Research Summary

Efficacy of infection control: Design and production of prototype for construction and automated washing and sterilization device development of cleaning and sterilization system without the necessity for the first disinfection by manual operation.

3. Result

Production of the prototype:
Washing and sterilization ability suitable for standard-precaution.
Washing condition sufficiently removing bacterial biofilm adhered to instruments. Sterilization level was also high.
The device has been confirmed to be usable as a safe device in the environment.

4. For Application

The washing and sterilization device matches the standard-precaution and reduced environmental loading. Diffusion among and contribution to medical institutions requiring a washing device for infection control are considered.

Competitive Advantages

Medical washes in which the disinfection by washing and chemicals is possible has already been developed. The device in this study disinfects and sterilizes at autoclave level by utilizing normal pressure superheated steam for excellent cleaning ability without chemicals.

Patent/Journal/Award

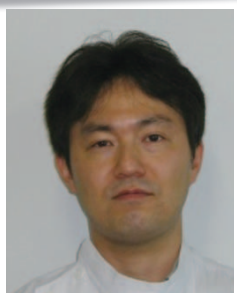
Patent, 1: Washing Sterilization Device, Japanese Patent Unexamined Publication No. 2008–188044
2: Sterilization Device, Japanese Patent Unexamined Publication No. 2008–188045

URL

Life Science

Functional Diagnosis of Cancers by the Surface Plasmon Resonance Biosensor

Keywords Surface Plasmon Resonance, Cancer, Cellular Function



Takaaki HIRAGUN

Department Natural Science Center for Basic Research and Development

Title Assistant Professor

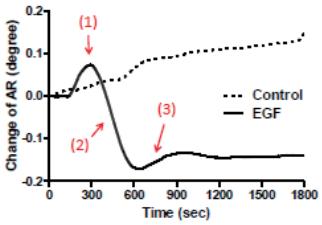
E-mail hiragunt@hiroshima-u.ac.jp

Field Dermatology, Diagnostic Oncology

Outline

1. Background

Surface plasmon resonance (SPR) biosensor detects intracellular signaling events of living cells as a change of angle of resonance (SPR signal) in real time without any labeling. The diagnosis of cancers are made by histopathological observations, although cancers are characterized by their behaviors (e.g. limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis).

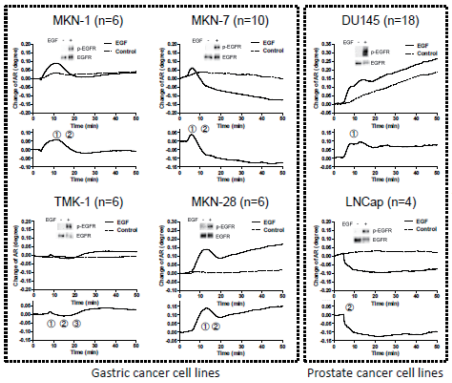


2. Research Summary

Carcinoma or non-carcinoma cell lines were seeded onto the sensor chips and stimulated with epidermal growth factor (EGF). The changes of angle of resonance in response to EGF were monitored with the SPR biosensor.

3. Result

The activation of non-tumorigenic HaCaT cells and one out of six carcinoma cell lines showed a full triphasic change of AR. In contrast, five out of the six cell lines showed mono- or bi-phasic change of AR.



4. For Application

Clinical application to evaluate the cellular function of circulating tumor cells (CTCs) with SPR imaging apparatus (Yanase Y, Hiragun T, et al. Biosens Bioelectron, 2010).

Competitive Advantages

Recently, CTCs have been used to predict the prognosis and the evaluation of anti-cancer therapies, although the cellular function of CTCs could not be tested. The evaluation of cellular functions of CTCs with SPR biosensors must contribute to the development of novel diagnosis of malignant tumors.

Patent/Journal/Award

Hiragun T, et al. Biosens Bioelectron. 32: 202–7, 2012.

URL

Life Science

Risk Management in Medical Practice

Keywords Risk Management, Clinical Medicine

Tooru HIYAMA

Department Health Service Center
Title Assistant Professor

E-mail tohiyama@hiroshima-u.ac.jp
Field Clinical Medicine, Gastroenterology, Social Medicine

Outline

1. Background

Clinical medicine contains various kinds of risks, and the effort to reduce the risks minimally is important. Medical malpractice litigations can be used as case studies for health care workers. Therefore, examining the litigation cases can be one of the risk management activities.

2. Research Summary

We investigate Japanese medical litigation cases from view point of risk management, and feedback important points to health care workers to prevent medical malpractice.

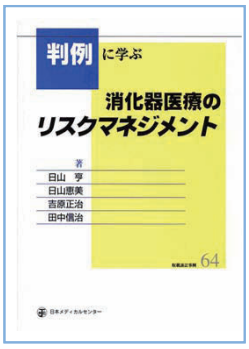
3. Result

We have published papers on medical risk management:

1) Hiyama T, et al. Change in malpractice claims in Japanese gastroenterological practice. Am J Gastroenterol 107: 143–4, 2012.
2) Hiyama T, et al. Trend in Japanese malpractice litigation involving gastrointestinal endoscopy. Am J Gastroenterol 104: 251–2, 2009. etc.

We also have published 4 books on medical risk management for health care workers (right figure). Now, we are preparing new book.

Published books



4. For Application

We are trying to develop the education system using internet for prevention of medical malpractice.

Competitive Advantages

One of the major risk management activities is incident/accident reports. However, sometimes, the reports are useless for insufficient informed consent, etc. We can discuss the contents of informed consent by case studies using malpractice litigation cases. The case studies can be one of powerful risk management activities.

Patent/Journal/Award

Academic Encouragement Award, Japanese Society of Gastroenterological Cancer Screening, 2006.

URL http://home.hiroshima-u.ac.jp/tohiyama/

Life Science

Generation of Model Mice for Human Diseases and its Application for Development of Novel Therapies

Keywords Genetically-engineered Mice (Transgenic Mice, Knockout Mice, Knockin Mice), ES (Embryonic Stem) Cells, Disease Model Mice

Hiroaki HONDA
Department Research Institute for Radiation Biology and Medicine
Title Professor
E-mail hhonda@hiroshima-u.ac.jp
Field Experimental Animal, Tumor Biology, Hematology, Molecular Biology

Outline

1. Background

A number of gene mutations have been identified in human diseases. However, to investigate whether the identified gene mutations are responsible for disease initiation, it is necessary to express the target genes in animals, such as in mice, and to see whether the disease phenotypes are recapitulated. In addition, these mice can be used as valuable disease models not only for investigating the disease pathogenesis but also for developing rational therapies. To this aim, we have generated a number of genetically-engineered mice by using developmental engineered techniques.

Fig 1 DNA ingection

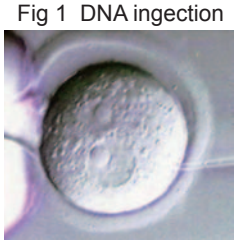


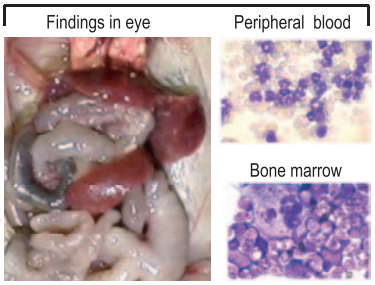
Fig 2 ES Cell ingection

2. Research Summary

The techniques for generating genetically-engineered mice can be classified as two groups; i) one is to inject DNA solution into pronuclei of mouse eggs and is used to generate transgenic mice (Fig. 1), ii) the other is to inject homologously recombined ES (embryonic stem) cells into mouse blastocysts and is used to generate knock-out/knock-in mice (Fig. 2). Chimeric mice generated by the latter method are shown in Fig. 3. We establish various mouse lines by using these techniques, analyze phenotypes of the mice, and clarify the pathogenesis for the diseases.

Fig 3 Chimera mouse

Fig 4 Chronic myelo-monocityic leulemia model mouse



3. Result

We generated transgenic mice for p210BCR/ABL, a chimeric gene believed to initiate chronic myelogenous leukemia (CML), and succeeded in establishing a mouse line exhibiting the CML phenotype (Fig. 4). This shows the first success in generating a transgenic model for CML, and since this transgenic model stably transmits to the progeny and reproducibly exhibits CML phenotype, it has been distributed to a number of laboratories and used to investigate the pathogenesis of the disease. In addition, we have generated a number of different genetically-engineered mice in collaboration with domestic and foreign universities and institutes and analyzed the biological function of the target genes and their contribution to humans diseases.

4. For Application

Our research purpose is to analyze disease pathogenesis and to develop rational therapies against diseases by generating model mice, thus our research theme will contribute to medical and pharmaceutical industries.

Competitive Advantages

By using genetically engineered techniques, we can generate various mutant mouse lines, such as those with gain-of-function, with loss-of-function, and harboring a point mutation in genes of interests. In addition, we can visualize the target gene product by inserting a fluorescent gene. With these techniques, we can investigate biological functions of target genes and their contribution to human diseases, which can not be analyzed by conventional molecular and cellular experiments.

Patent/Journal/Award

Journals: 1st, last, or corresponding author; PNAS (2011), J Immunol (2010), Hepatology (2010), Dev Biol (2010), Oncogene (2010, 1999), Blood (2000, 1999, 1998, 1995, 1994), Oncogene (2008), Nature Genet (1998), Coauthor; Nature (2009), Immunity (2008), Human Mol Genet (2005), J Exp Med (2004), Mol Cell Biol (2004, 2000, 1997), Blood (2003, 1999, 1998), J Biol Chem (2002, 1997), EMBO J (2000), PNAS (1998)

Awards: 1) Young Investigator Award of the Japanese Society of Hematology (1995)
2) Young Investigator Award of the Japanese Society of Internal Medicine (1998)
3) Young Investigator Award of the Japanese Cancer Association (2000)
4) Human Frontier Science Program Organization Long-Term Fellowship Award (2000)
5) Eminent Scientist of the Year 2011, International Research Promotion Committee (2011)

Others: Most of the genetically-engineered mice we generated have been deposited in RIKEN BioResource Center (RIKEN BRC) and can be distributed to researchers in domestic and foreign Universities and Institutes. Please refer to "http://www.brc.riken.go.jp/lab/animal/en/" for details.

URL http://home.hiroshima-u.ac.jp/sosai/top.html

Life Science

Cure Rate Improvement of Intractable Hematopoietic Malignancies by Transplantation

Keywords Transplantation

Hideo HYODO

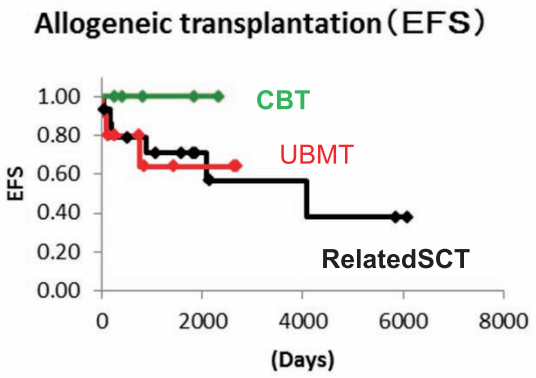
Department Research Institute for Radiation Biology and Medicine
Title Associate Professor

E-mail hyodo@hiroshima-u.ac.jp
Field Hematology

Outline

1. Background

Transplantation therapy may be cure for intractable hematopoietic malignancies. However, allogeneic transplantation treatments often leave the serious problem to the quality of life after transplantation and early treatment-related mortality rate is higher than usual chemotherapy. Although this method has been clinically available, many problems are not yet clear. What is optimal conditioning regimen on each stages of disease? How do we choose correctly in many sources of stem cells? Can we manage to transplant up to what age?. How should we do beyond organ disorders?



2. Research Summary

Hiroshima University Hospital has been certified facility from Bone Marrow and Cord Blood Banks. We have carried out stem cell transplantations from related donors but unrelated donors also. We believe to improve the cure rate for intractable hematopoietic malignancies by transplantation.

3. Result

We suggest the possibility of long-term survival in patients with Philadelphia chromosome positive acute lymphocytic leukemia by autologous transplantation using stem cell fraction with undetectable small residual disease. Those patients cannot find out any donors . We has accomplished leaving survival 98% rate from our clean rooms in allogeneic transplantation including CBT.

4. For Application

This method is clinically available. The cure rate will be expected to improve by the following.

Transplantation combined new of chemotherapy agents and immunosuppressive agents may reduce the recurrence rate of hematological malignancies.

New of antibacterial agents and antifungal agents may reduce the mortality rate related transplantation .

Competitive Advantages

Allogeneic transplantation is effective for hematological malignancies due to immune therapy.

Patent/Journal/Award

URL

Life Science

An Electromagnetophysiological Study on Epileptogenic Zones and Epileptic Spikes Using Intracranial Electroencephalography and Magnetoencephalography (MEG) in Epilepsy Surgery

Keywords Epilepsy Surgery, Intracranial Electroencephalography (EEG), Intractable Epilepsy, Magnetoencephalography (MEG)

Koji IIDA

Department Hiroshima University Hospital

Title Associate Professor / Lecturer

E-mail iidak@hiroshima-u.ac.jp

Field Neurology, Neurosurgery

Outline

1. Background

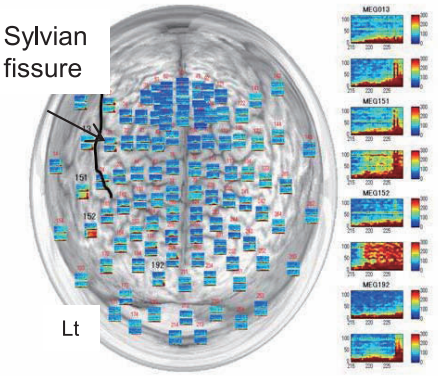
Recent advancement of neuroimaging technique has reduced a necessity of invasive intracranial EEG for epileptogenic localization in many patients with intractable epilepsy, however, in some cases, visual inspection even on ictal IVEEG recording may be insufficient for demarcation of cortical resection with epileptogenesis. It is desirable to establish a new technique with less invasiveness for epileptogenic localization.

2. Research Summary

Ⅰ. MEG equivalent current dipole (ECD) characterizations by comparing the characterized ECDs with MRI and scalp EEG

Ⅱ. Originally developing gradient magnetic-filed topography (GMFT) for MEG to visualize the dynamic change of gradient magnetic fields for interictal epileptic discharges

Ⅲ. Focusing on high-frequency oscillation (HFO) detected in IVEEG using multiple-band frequency analysis (MBFA) and analysis of ictal MEG frequency with MBFA and plotting a time-frequency map of the individual brain surface.



Time-frequency map (frequency-band: 0-110 Hz) of each MEG-sensor and superimposed all maps onto individual brain-surface MR images (deployed using Mercator projection) to visualize dynamic changes and distributions of HFO (MEG channel 152).

3. Result

GMFT may complement ECD analysis for preoperative evaluation and ictal MEG-derived HFO distributions coincided with HFO distributions in IVEEG.

4.For Application

These findings may be useful in locating epileptic zones, and facilitate clarification of the epileptic network in epilepsy surgery. Our original technique of MEG data analysis may be more practical in less-invasive epileptogenic localization.

Competitive Advantages

Our new technique (GMFT and time-frequency map (deployed using Mercator projection) is highly original and promising, compared with other MEG-data analysis method.

Patent/Journal/Award

Ann. Rep. Jpn. Epi. Res. Found. Award (2011; 22: 9–14): An electromagnetophysiological study on epileptogenic zones and epileptic spikes using intracranial electroencephalography and magnetoencephalography in epilepsy surgery

URL

Life Science

Development of New Antiviral Therapy Using a Chimeric Mouse Human Hepatocytes Infected with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)

Keywords Hepatitis Virus, Human Hepatocyte, Chimeric Mice

Michio IMAMURA

Department Hiroshima University Hospital

Title Assistant Professor

E-mail mimamura@hiroshima-u.ac.jp **Field** Internal Medicine, Gastroenterology

Outline

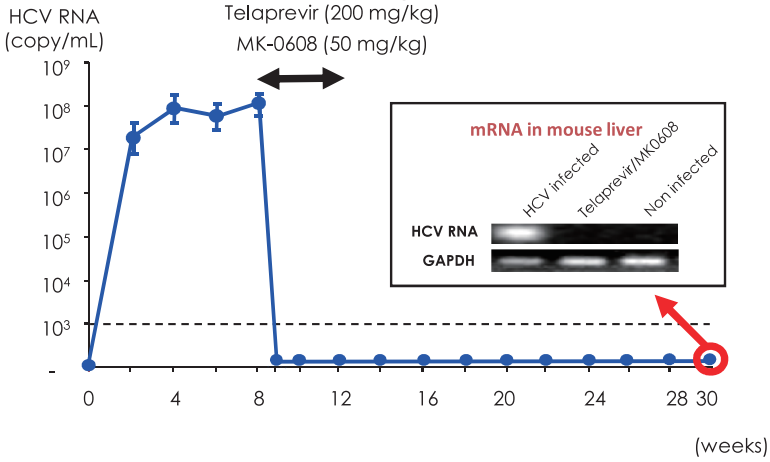
1. Background

The development of new anti-HCV drugs has been severely restricted by the absence of a cell culture system, and the lack of a small animal model. Chimpanzee was the only useful animal for the study of HBV and HCV until recently, although the availability of this model is severely restricted.

2. Research Summary

HBV/HCV-infected mice have been developed by inoculating HBV/HCV-infected human serum into chimeric urokinase-type plasminogen activator (uPA)-severe combined immunodeficiency (SCID) mice with engrafted human hepatocytes (chimeric mice). Using this animal model, we have done the translational research to discover and develop new therapies.

MK-0608 and telaprevir combination treatment eliminates virus in HCV-infected mice.



3. Result

All mice treated with telaprevir and MK-0608 combination therapy for four weeks became negative for HCV RNA one week after the beginning of the therapy and remained negative after 18 weeks. Negative testing for HCV RNA in mouse liver by nested PCR 18 weeks after cessation of the therapy strongly suggests that HCV was completely eliminated from the mouse. Eradication of HCV from mice with only four weeks of therapy without interferon points the way to future combination therapies for chronic hepatitis C patients.

4. For Application

- The fields of medical and biotechnology
- Analysis of the mechanism of infectivity and replication of HBV and/or HCV
- Development of new antiviral therapy for patients with HBV and/or HCV

Competitive Advantages

This animal model is the only small animal model infected with HBV and/or HCV. HBV/HCV-Infected engrafted human hepatocyte in chimeric mice keep the high viral titer in mice serum for several months.

Patent/Journal/Award

Sainz B Jr, et al. ***Nat Med*** 2012; 18: 281–5, Hiraga N, et al. ***Hepatology*** 2011; 54: 764–71
Hiraga N, et al. ***Hepatology*** 2011; 54: 781–8, Saeed M, et al. ***Hepatology*** 2011; 54: 425–33
Ohara E, et al. ***J Hepatol*** 2011;54: 872–8, Ohira M, et al. ***J Clin Invest*** 2009; 119: 3226–35
Matsumura T, et al. ***Gastroenterology*** 2009; 137: 673–81

URL http://home.hiroshima-u.ac.jp/naika1/e/

Life Science

Functional Analysis of RSC Chromatin-Remodeling Complex in Budding Yeast

Keywords Chromatin Remodeling, RSC, Transcriptional Regulation

Yuko IMAMURA

Department Graduate School of Advanced Sciences of Matter

Title Assistant Professor

E-mail yukoima@hiroshima-u.ac.jp Field Molecular Biology, Agrochemistry, Basic Biology

Outline

1. Background

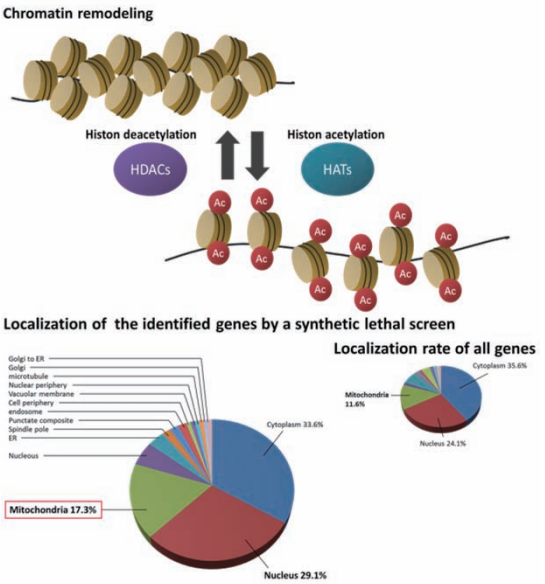
RSC chromatin-remodeling complex has crucial roles in nuclear processes including transcription, DNA replication, DNA repair, recombination and chromosome segregation.

2. Research Summary

We performed a synthetic lethal screen with the temperature-sensitive mutant of NPS1 which was a ATPase subunit of RSC complex. As a result of the screening, about 20% of the identified genes were mitochondria associated genes. Therefore, we investigated relations between RSC and mitochondria.

3. Result

RSC mutations exhibited defects in mitochondria and resulted in a reduction of mitochondrial metabolism and inhibition of mitochondria-dependent autophagy, a shorter lifespan.



4. For Application

RSC complex in S.cerevisiae is evolutionarily conserved through eukaryotes. PBAF complex of mammalian cells known as a tumor suppressor is an ortholog of RSC. It is suggested that our findings of RSC complex indicate new functions of PBAF complex in carcinogenesis.

Competitive Advantages

Relationships between RSC complex and mitochondria have not been reported previously. This study is possible to elucidate novel physiological functions of chromatin remodeling.

Patent/Journal/Award

URL http://home.hiroshima-u.ac.jp/mbiotech/tsuchiya_lab/Top.html

Life Science

Investigation of Interaction of Cancer Stem Cell to Mesenchymal Stem Cell in Oral Cancer

Keywords Cancer, Stem Cell

Yasutaka ISHIDA

Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail yaishida@hiroshima-u.ac.jp
Field Dentistry, Oral Surgery

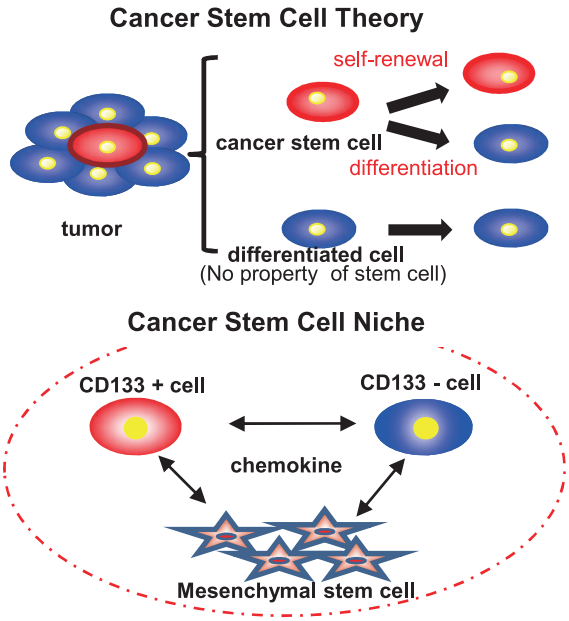
Outline

1. Background

It is thought that mesenchymal stem cell derived from human bone marrow affects invasion and metastasis of cancer cell in oral cancer, because oral cancer is close to jaw bone.

2. Research Summary

We separated CD133+ cell from oral squamous cell carcinoma cell established our laboratory by magnetic cell sorting. We collected conditioned medium from mesenchymal stem cell derived from human bone marrow cultured in serum free condition. CD133+ cell was cultured in serum free medium to which conditioned medium of mesenchymal stem cell was added, and influence on biological property of CD133+ cell was analyzed. We investigated chemokines in conditioned medium of mesenchymal stem cell, and analyzed effect of chemokines facilitated in mesenchymal stem cell on biological property of CD133+ cell.



3. Result

It is elucidated that chemokines derived from mesenchymal stem cell play an important role in sustaining biological property of CD133+ cell.

4. For Application

It is thought that this result contributes to the development of novel therapy targeting cancer stem cell.

Competitive Advantages

This research is conducted in serum-free condition. Effect of liquid factor derived from serum is excluded.

Patent/Journal/Award

URL

Life Science

A Study on the Architectural Planning on Children's Home

Keywords Facility Planning, Children's Home, Downsizing the Living Unit

Aya ISHIGAKI

Department Graduate School of Engineering

Title Assistant Professor

E-mail isgkay@hiroshima-u.ac.jp

Field Architectural Planning

Outline

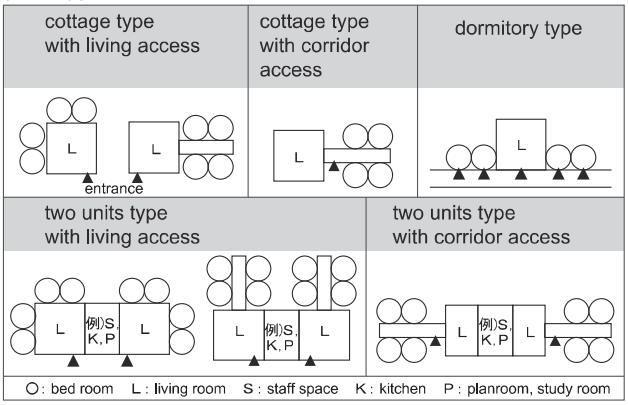
1. Background

The number of the children out of home care is increasing these days in Japan, and most of them are abused, suffer from family trouble or have some developmental disability. In order to support their physical and mental development, homely environment is important.

2. Research Summary

To examine the actual condition of downsizing the living unit in children's home, the questionnaire survey was conducted for 205 children's homes. Also, we conducted some field surveys on the cottage-type children's home to examine the relationship among space, communication, and the effectiveness of therapy.

prototype of children's home



3. Result

From the survey of the actual condition of downsizing the living unit in children's home, the prototype of the living unit plan is characterized. From the field surveys on the cottage-type residential center to examine the relationship among space, communication, and the effectiveness of therapy, it can be said that the characteristics (such as floor space, the number of children, and the organization of the space) contributed to a better condition for the milieu therapy.

4. For Application

To provide consultation on children's home construction or reconstruction project.

Competitive Advantages

To provide consultation on children's home construction or reconstruction project.

Patent/Journal/Award

MEANINGS OF SPACE OF COTTAGE-TYPE RESIDENTIAL CENTER IN MILIEU THERAPY FOR EMOTIONALLY DISTURBED CHILDREN, J.Archit. Plann, AIJ, No.582, 17–23, 2004

A STUDY ON THE CONDITION OF DOWNSIZING THE LIVING UNIT IN CHILDREN'S HOME, J.Archit. Plann, AIJ, Vol.77 No.671, 19–25, 2012

URL

Life Science

Health Promotion and Prevention of Sports Injuries

Keywords Health, Fitness

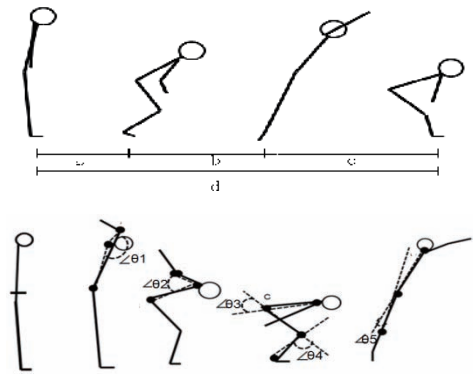
Yoshimasa ISHII

Department Graduate School of Education
Title Associate Professor
E-mail yoishii@hiroshima-u.ac.jp
Field Sports Medicine, School Health

Outline

1. Background

In recent years, to perform instruction from a scientific standpoint is desired by progress of sports science at the school and the sports field. The measurement under sporting activities becomes easy and analysis of operation of the body is available by development of new computer software, and they are becoming a general technique.



Biomechanical analysis of standing long jump

2. Research Summary

- Investigating about the relation between the speed change and the range of joint motion at the time of sport movement, and evaluation from a viewpoint of biomechanics.
- Examining the body reaction and operation in the method of training a handicapped child, and a person.
- Investigation about the consciousness about middle and old age people's health.

3. Result

- The study of relation between kinematic parameters of the trunk and upper limb and performance with the standing long jump. Journal of Training Sciences for Exercise and Sport. 23 (1) 77–85, 2011
- The study of disabled persons on the study effects of the standing jump. Japanese Journal of Support System for Developmental Disabilities. 10 (1) 43–49, 2011

4. For Application

School, Rehabilitation

Competitive Advantages

Patent/Journal/Award

URL

Life Science

Gene Expression Profiles of Idiopathic Interstitial Pneumonias: Identification of Disease-specific Diagnostic Markers and Molecular Therapeutic Targets

Keywords Idiopathic Pulmonary Fibrosis, Microarray, Biomarker

Nobuhisa ISHIKAWA

Department Institute of Biomedical & Health Sciences

Title Associate Professor / Lecturer

E-mail nobuhi@hiroshima-u.ac.jp

Field Pulmonary Medicine

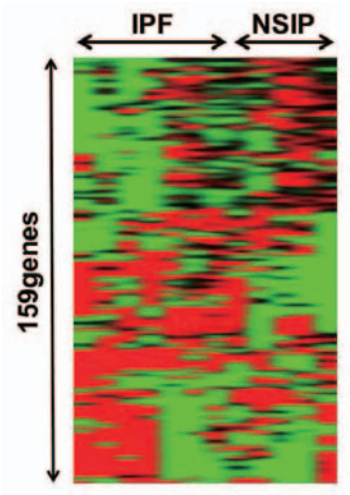
Outline

1. Background

Idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) are characterized by alveolar epithelial damage and inflammatory responses that lead to fibroblast proliferation and, ultimately, to loss of normal pulmonary architecture and function. Differential diagnosis between IPF and NSIP may be difficult. The molecular mechanisms underlying idiopathic interstitial pneumonias (IIPs) remain unclear.

2. Research Summary

This study aimed to elucidate the mechanisms underlying IIPs and identify disease-specific diagnostic markers and molecular therapeutic targets. The study included 12 patients with IIPs (IPF, 7 patients; NSIP, 5 patients). RNA was extracted from frozen lung specimens from the study population and was profiled using Illumina Human WG-6 v3 BeadChips. Gene ontology functional annotations were investigated in the genes upregulated in IIPs.



3. Result

Evaluation of 48,000 transcripts in the expression profiles helped identify 1594 transcripts that were commonly upregulated in lung tissues from IIP patients compared to those from normal control subjects. The transcriptional profiles of IPF and NSIP were unexpectedly similar. Lungs with IIP were characterized by increased expression of transcripts associated with cell cycle, ABC transporters and p53 signaling pathways.

4. For Application

The current data provide valuable information on the molecular mechanism underlying pulmonary fibrosis in IIP patients. Additionally, several potentially promising and novel diagnostic biomarkers as well as therapeutic targets have been identified for IIPs.

Competitive Advantages

The genome-wide microarray analysis enabled us to obtain comprehensive gene expression profiles related to detail phenotypic and biological information in several diseases. We and other researches, in fact, have performed gene expression profile analysis of lung cancers, and identified various applicable targets for development of new diagnostic tools and therapeutic strategies through subsequent systemic approach combined with high throughput screening systems. However, to our best knowledge, gene expression analysis of pulmonary fibrosis, especially in Japanese, had not been studied well. The main goal of this study was to clarify the mechanisms related to IIPs, and to identify disease specific markers as well as molecular target.

Patent/Journal/Award

Awards of the JCA (Japanese Cancer Association) in 2008.

URL

Life Science

New Method for Gastric Cancer Screening by Serum Markers

Keywords Gastric Cancer, Gastritis, Helicobacter Pylori

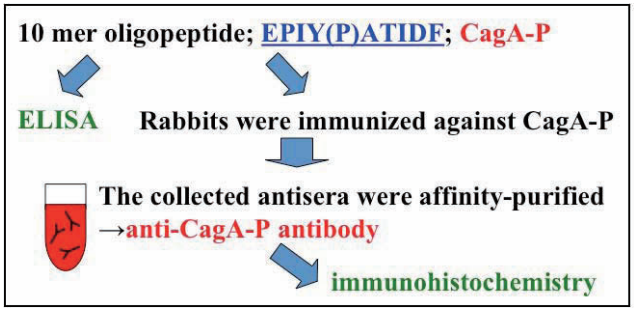
Masanori ITO

Department Institute of Biomedical & Health Sciences
Title Associate Professor / Lecturer
E-mail maito@hiroshima-u.ac.jp
Field Gastroenterology

Outline

1. Background

Effective screening system against gastric cancer is essential clinical problem especially in Japan,



2. Research Summary

Helicobacter pylori (*H. pylori*) causes chronic inflammation, and a toxic peptide, CagA, plays an important role in the clinical outcome. Tyrosine phosphorylation of Glu-Pro-Ile-Tyr-Ala (EPIYA) motif in CagA plays critical role in the morphological transformation of cells. We synthesized an oligo-peptide (CEPIY(P) ATIDF; CagA-P) designed from East Asian CagA-specific EPIYA-D site as an antigen and examined the titer of anti-CagA-P antibody by an enzyme-linked immunosorbent assay (ELISA) in Japanese patients

3. Result

We confirmed that CagA-P is an antigen-peptide against the host and there is a relationship between the titer of anti-CagA-P antibody and histological findings of gastritis. Using our ELISA system, it was possible to quantitatively evaluate tyrosine phosphorylation of the CagA protein.

4. For Application

For clinical use, some improvements may be needed, especially in effective cut-off value and experimental reproduction.

Competitive Advantages

Patent/Journal/Award

Takata S, Ito M et al. JG, 2009
Wada Y, Ito M, et al. Digestion 2010

URL

Life Science

Clarification of Signaling Pathway Controlling Breast Cancer

Keywords Breast Cancer, Wnt Signaling, Hypoxia Response

Takayuki KADOYA

Department Hiroshima University Hospital
Title Associate Professor / Lecturer
E-mail takayukikadoya@gmail.com
Field General Surgery

Outline

1. Background

Carcinogenesis and metastasis of breast cancer are controlled with various signaling pathway. Recently, Molecular targeted therapies have been developed for breast cancer(ie; trastuzmab)

2. Research Summary

Our aim of research is to clarify the importance of Wnt signaling and hypoxia signaling pathway on breast cancer.
(1) The relation of Wnt5a expression and prognosis of breast cancer
(2) Hypoxia response of breast cancer tissue (HIF, VEGF expression) and prognosis of breast cancer

3. Result

Our research has just started since April in 2011, we have prepared for immunohistochemistry of tissue and research of cell biplogy.

4. For Application

Targeted molecule of breast cancer theraphy

Competitive Advantages

Japan-North America Medical exchange Foundation 2003

K.Nakayama **T. Kadoya**,, Z.Ronai et al: Siah2 regulates stability of prolyl-hydroxylases, controls HIF1 alpha abundance, and modulates physiological responses to hypoxia. Cell 177(7): 941–952, 2004.

T. Kadoya, A. Kikuchi et al: Desumoylation activity of axam, a novel axin-binding protein, Is involved in downregulation of β-Catenin. Molecular and Cellular Biology 22(11): 3803–3819, 2002.

T. Kadoya, A. Kikuchi et al: Inhibition of Wnt signaling pathway by a novel axin-binding Protein. Journal of Biological Chemistry 275(47): 37030–37037, 2000.

Patent/Journal/Award

URL http://home.hiroshima-u.ac.jp/genge/04staff/staff.html

Life Science

Remarkable Factors Related to Preventing Relapse of Deciduous Anterior Crossbite

Keywords Deciduous Anterior Crossbite, Saddle Angle, Study Model Analysis, Cephalometric Analysis

Yasutaka KAIHARA

Department Hiroshima University Hospital
Title Assistant Professor
E-mail kaihara@hiroshima-u.ac.jp
Field Pediatric Dentistry

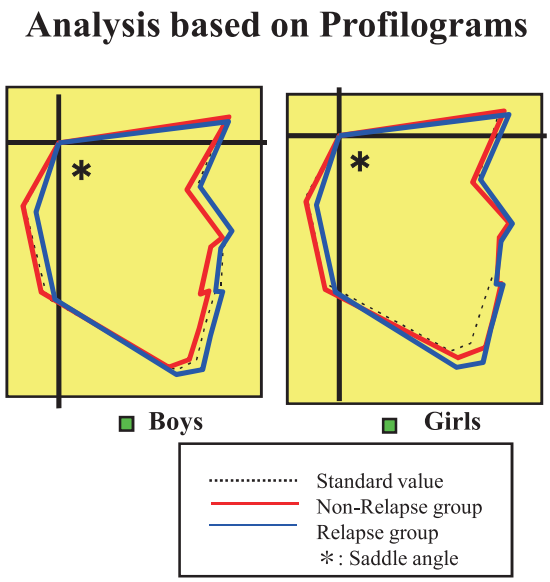
Outline

1. Background

The mandible is protrusive even in the late deciduous dentition and becomes more protrusive with time, making the discrepancy between the upper and lower jaws progressively more severe 5). Therefore, it seems desirable to restore deciduous anterior crossbite as early as possible. However, despite the correction of deciduous anterior crossbite, the patients may develop crossbite again and future orthodontic treatment may be required. For this reason, in treating deciduous anterior crossbite, determining the optimal time to start treatment and predicting the prognosis of treatment are very important.

2. Research Summary

In the present study, we investigated the pre-treatment morphological characteristics of craniofacial complex and dentition of children with deciduous anterior crossbite who showed favorable prognoses and avoided relapse even after growth and development were completed.



The subjects with deciduous anterior crossbite were divided into those without relapse and those with relapse and these two groups were compared using their lateral cephalometric radiographs and study models taken at first examination.

3. Result

This retrospective study indicates that early proactive treatment for deciduous anterior crossbite is considered suitable for children with the following characteristics.: (1) There was no family history of anterior crossbite. (2) There were no significant differences from the standard values in the width or length of mandibular dental arch. (3) On angular analysis, the variable with the most conspicuous difference between the non-relapsed prognosis group and relapse group was the NSAr angle (saddle angle). The value of this angle in the non-relapsed prognosis group was close to the standard value. This retrospective study indicates that early proactive treatment for deciduous anterior crossbite is considered suitable for children with the above characteristics.

4. For Application

Competitive Advantages

Patent/Journal/Award

URL

Life Science

Long-term Tooth Cryopreservation by Use of CAS Freezer

Keywords Cryopreservation, Periodontal Ligament, CAS Freezer

Masato KAKU

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail mkaku@hiroshima-u.ac.jp

Field Orthodontic

Outline

1. Background

Tooth autotransplantation is a useful procedure for recovering occlusal function by replacement of missing teeth. Wisdom teeth, impacted teeth and unnecessary teeth that are extracted for orthodontic treatment are mainly used as donor teeth. However, sometimes patients may not have a donor tooth available because it was previously extracted. To solve this problem, we planned to develop a teeth cryopreservation systems.

2. Research Summary

Human periodontal ligament (PDL) cells were frozen in 10% dimethyl sulfoxide (Me2SO) using a programmed freezer with a magnetic field (CAS). We compared gene expression in human PDL cells cultured from teeth immediately after extraction and from teeth cryopreserved for 3 days, and we examined periodontal healing after replantation of a rat incisor that was cryopreserved by CAS.

3. Result

A 0.1mT of a magnetic field, a 15-min hold-time, and a plunging temperature of -30°C led to the greatest survival rate of PDL cells. There was no difference in the mRNA expression of collagen type I between the cryopreserved group and the control group. There was no progressive root resorption in the rat teeth that were replanted after cryopreservation.

4. For Application

We have established “teeth bank” and try to develop other cell and tissue bank.

Competitive Advantages

A magnetic field prevents the formation of intracellular ice crystals by preventing the cluster of water molecules from growing by causing it to vibrate during freezing.

Patent/Journal/Award

Kaku et al., Cryopreservation of periodontal ligament cells with magnetic field for tooth banking. Cryobiology, 61, 73–78, 2010.

Abedini et al., Effects of cryopreservation with a newly-developed magnetic field programmed freezer on periodontal ligament cells and pulp tissues. Cryobiology, 62, 181–187, 2011.

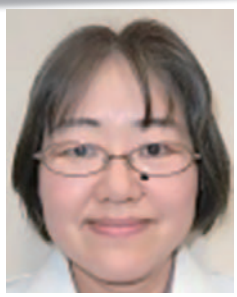
Kamada et al., In-vitro and in-vivo study of periodontal ligament cryopreserved with a magnetic field. Am J Orthod Dentofacial Orthop., 140, 799–805, 2011.

Autotransplantation of cryopreserved tooth: The 69th Japanese Orthodontic Society, poster award, 2010.

URL http://teethbank.jp/

Life Science

Characterization of Mesenchymal Stem Cell for Regenerative Therapy



Keywords Mesenchymal Stem Cell, Cell Culture, Cell Proliferation, Regenerative Therapy

Masami KANAWA

Department Natural Science Center for Basic Research and Development

Title Assistant Professor

E-mail mfuku@hiroshima-u.ac.jp

Field Dentistry

Outline

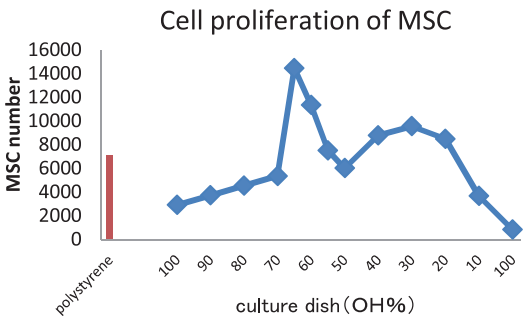
1. Background

It is necessary to clarify the culture method and property of MSC, useful cells for transplant, because the culture methods MSC are not yet unified.

2. Research Summary

MSCs are isolated from bone marrow aspiration after informed consent. Cultured MSCs are cryopreserved, and are deposited to RIKEN BioResource Center.

Growth potential of MSCs that were cultured on chemical defined dish using serum-free medium were examined



3. Result

I was able to contribute to offering MSC for studies to domestic and overseas researcher widely.

URL: http://www.brc.riken.jp/lab/cell/hms/search_hms.shtml

The chemical composition of the culture dish which was most suitable for growth condition of the MSC became clear.

4. For Application

To date, culture dishes made of polystyrene are used for various cells, but it is unidentified whether they are suitable to culture of each cells. Therefore, it is useful to examine chemical composition of the dish which is most suitable for culture of MSC.

Competitive Advantages

It is thought that chemical defined dish can contribute to provide the stable and safety culture technology of MSCs for regenerative medicine..

Patent/Journal/Award

J Tissue Eng Regen Med, Stem Cells Dev.

URL

Life Science

Effect of Cholesterol and its Biosynthetic Precursors on the Cause of BRONJ

Keywords BRONJ, Cholesterol Synthesis

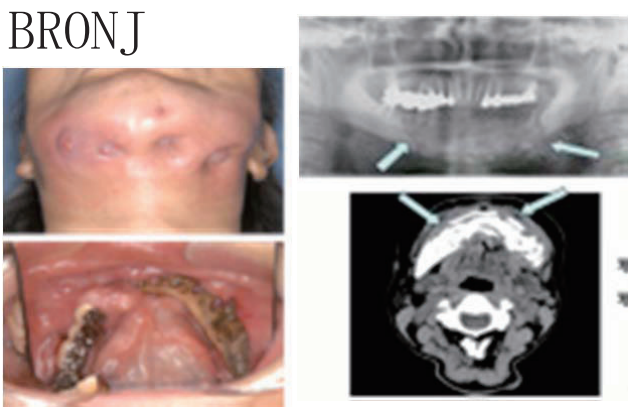
Taku KANDA

Department Hiroshima University Hospital
Title Assistant Professor
E-mail kantaku@hiroshima-u.ac.jp
Field Oral Surgery

Outline

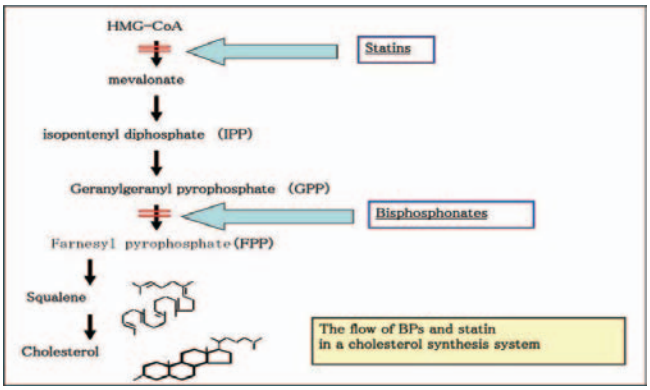
1. Background

The bisphosphonate (BPs) which act on a sterol synthesis course are widely prescribed for the patients with osteoporosis, hypercalcemia of malignant tumor, and bone transition.
After reporting on the jawbone necrosis case relevant to BPs in 2003, there are increasing number of reports on multiple bone exposure and critical jawbone necrosis cases of patients who took BPs in their dental care.



2. Research Summary

In this research, we analyze using a serum-free-culture system the influence on the multiplication, specialization, and sterol synthesis system which BPs exert on osteoblast, chondroblast and osteoclast. It aims to clarify the mechanism of bone resorption control or a bone development action of BPs and the mechanism which brings a necrosis specifically to a lower jaw and an alveolar bone. We aim at the new prevention to BRONJ, and development of a cure.



3. Result

We report the result of research about the influence which the cholesterol has in multiplication and specialization of a cartilage cell, and we have established the experiment system about a cartilage system cell and its cholesterol performance analysis.

4. For Application

The pathogenic mechanism of BRONJ is unknown. Our research is useful to enhance the knowledge of the BPs method to a malignant tumor patient or an osteoporosis patient.

Competitive Advantages

This research aims to compare the influence of BPs on osteoblast cell, chondroblast cell and osteoclast with the influence of the statin drugs which act on a cholesterol synthesis course in a serum-free-culture system, to attain the suitable method of prescribing BPs for the patient, new development or therapeutic substitution method of a cure, and an auxiliary cure.

Patent/Journal/Award

URL

Life Science

Research on Functions of a New Protein Regulating Energy Metabolism

Keywords Metabolic Syndrome

Takashi KANEMATSU

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail tkanema2@hiroshima-u.ac.jp

Field Pharmacology

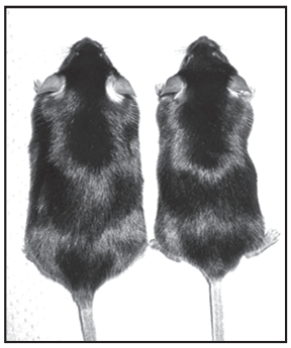
Outline

1. Background

Metabolic syndrome is a modern disease that has become a serious social problem. Many scientists are studying the mechanisms of metabolic syndrome, but our understanding remains incomplete.

2. Research Summary

We analyzed a PLC-related catalytically inactive protein (PRIP) knockout mouse and found that the mice were hyperphagic but thin.



WT KO

3. Result

We studied the energy mechanisms influenced by PRIP in knockout mice and characterized a pathogenic mechanism of metabolic syndrome.

4. For Application

Development of drug which regulates the PRIP functions.

Competitive Advantages

PRIP is a new intracellular signaling molecule that we have identified.

Patent/Journal/Award

URL

Life Science

Antibody Arrays for Parallel Analysis of Surface Marker Expression

Keywords Regenerative Medicine, Stem Cells, Quality Control, Micro-processing, High-throughput Analysis

Koichi KATO

Department Institute of Biomedical & Health Sciences

Title Professor

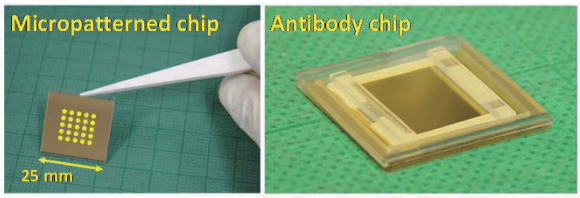
E-mail kokato@hiroshima-u.ac.jp

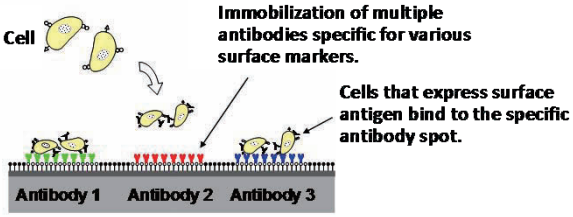
Field Biomedical Engineering / Nano- & Micro-technology / Dental Regenerative Medicine

Outline

1. Background

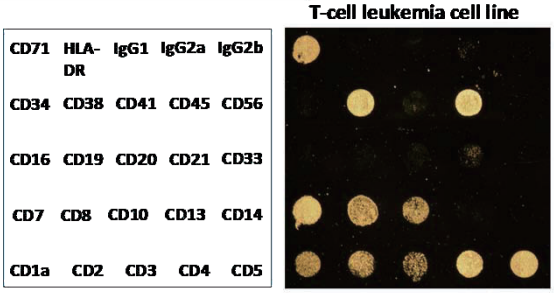
Cells for use in stem cell-based regenerative medicine must be thoroughly controlled before transplantation for safe and efficient treatments. We focused on the pattern of surface marker expression as one of the most important parameters for the characterization of heterogeneous populations containing cells at different differentiation stages. Although such analyses have been performed by flow cytometry, this conventional method is laborious and uneconomical.





2. Research Summary

Using a micro-processing technique, we fabricated biochips on which multiple antibodies to surface markers were arrayed in a site-addressable manner. When the antibody chips were subjected to binding assays using leukemia cell lines and mesenchymal stem cell lines, we could simply acquire the patterns of surface markers expressed on these cells. It was further demonstrated that the content of specific stem cells contained in a heterogeneous population can be quantitatively determined by immunologically staining intracellular markers in the stem cells bound to the antibody chips.



3. Result

The antibody chips enable us to analyze the pattern of surface markers more efficiently than the conventional flow cytometry does, providing a practical means for the quality control of cells used in stem cell-based transplantation therapy.

4. For Application

We expect collaboration with companies that take an interest in the applications of micro-processing technologies, antibody developments, and sensing devices to the establishment of infrastructure with regard to stem cell-based regenerative medicine.

Competitive Advantages

Antibody microarrays provide a new method to control qualitatively and quantitatively heterogeneous populations containing stem cells. This method enables higher throughput analysis and is more simple and convenient than the conventional flow cytometry.

Patent/Journal/Award

Japanese Patent No. 4336812, Anal Chem 79:8616–23 (2007), Biomaterials 28:1289–97 (2007); 26:4882–91 (2005); 26:687–96 (2005). The Award for Young Investigator of Japanese Society for Biomaterials, 2004.

URL http://home.hiroshima-u.ac.jp/bmt/home_j.html

Life Science

Novel Functions of Silk Protein, Sericin

Keywords Food Function, Blood Lipids, Blood Glucose, Colon Disease

Norihisa KATO

Department Graduate School of Biosphere Science

Title Professor

E-mail nkato@hiroshima-u.ac.jp

Field Agricultural Chemistry

Outline

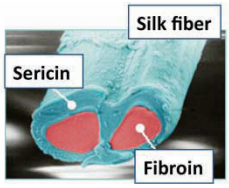
1. Background

Silk protein, sericin, is mostly removed from the cocoon and disposed of without any use when the cocoon is used for making silk textiles. Sericin is unique because it has a large amount of an amino acid, serine, and a protease-resistant property. Our discovery of the strong antioxidant function of sericin has led to a series of our studies to elucidate its novel functions. For example, dietary addition of sericin causes anti-colon cancer and ant-constipation effects. Furthermore, topical application of sericin to the skin suppresses skin UV-damage and carcinogenesis.

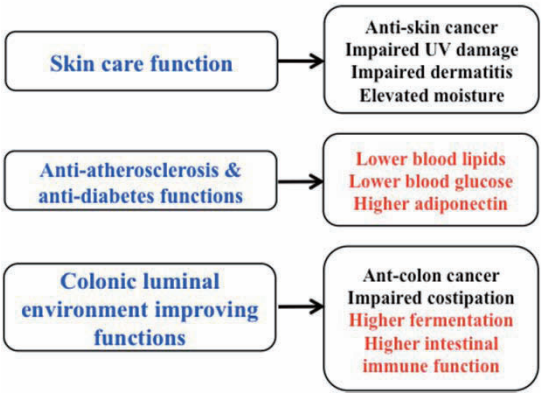
2. Research Summary

This study was conducted to examine the influence of dietary sericin on blood lipids and glucose and colonic luminal environment in rats fed a high-fat diet.

Figure



Novel Functions of Sericin



3. Result

This study demonstrated that dietary sericin suppressed blood triglyceride and cholesterol and blood glucose together with the elevation in blood adiponectin. Further, it was found that dietary sericin elevated intestinal fermentation by microflora and intestinal immune and barrier functions. The results imply the novel functions of sericin including anti-atherosclerosis, anti-diabetes, anti-colon cancer and anti-colitis functions (indicated with red letters in Figure).

4. For Application

Functional food, supplement, medicine and textile

Competitive Advantages

Discovery of novel useful functions of sericin which has been disposed. A model of development of novel functional protein.

Patent/Journal/Award

Journal:

1) Kato et al. Resistant protein; its existence and function beneficial to health. *J Nutr Sci Vitaminol* 48: 1 (2002).
2) Okazaki et al. Consumption of sericin reduces serum lipids, ameliorates glucose tolerance and elevates serum adiponectin in rats fed a high-fat diet. *Biosci Biotechnol Biochem* 74: 1534 (2010).
3) Okazaki et al. Consumption of a resistant protein, sericin elevates fecal immunoglobulin A, mucin, and cecal organic acids in rats fed a high-fat diet. *J Nutr* 141: 1975 (2011).

URL http://www.hiroshima-u.ac.jp/gsbs/kenkyu_syokai/serishin/index.html

Life Science

Regenerative Medicine Using Mesenchymal Stem Cells Expanded with Serum-free Media

Keywords Regenerative Medicine, Mesenchymal Stem Cells, Serum-free Media

Yukio KATO

Department Institute of Biomedical & Health Sciences
Title Professor
E-mail ykato@hiroshima-u.ac.jp
Field Functional Basic Odontology

Outline

1. Background

Mesenchymal stem cells (MSC) are useful in regenerative medicine, but expansion of MSC requires the presence of serum in culture medium, which may be contaminated with prions and viruses. In addition, serum batches markedly affect culture performance. So it was difficult to expand MSC in culture safely and consistently.

STK1, STK2, STK3

2. Research Summary

We examined the effect of various combinations of 80–90 compounds on proliferation of MSC under serum-free conditions. We also examined whether the serum-free media maintained the multipotency of MSC. We also examined tumor risk of MSC expanded with the serum-free media.

3. Result

We found that serum-free chemically defined media STK1–3 are useful in primary, passage, and differentiation cultures, respectively. They enhanced proliferation or differentiation of MSC at much higher levels than did medium containing 10% FBS.

4. For Application

STK1 and STK2 are now being used for MSC expansion in several hospitals and many universities. The sales are increasing every year. When these media get the approval from Government, application of MSC to regenerative medicine will become one of routine treatments for various diseases.

Competitive Advantages

STK enhances proliferation of MSC 100-to 1000-fold, and differentiation 2-to 10-fold. No serum-batch-dependent variation of culture performance and no cancer risk.

Patent/Journal/Award

Patents

1.Kato Y, Shao J. et al. Japanese Patent No. 4385076, PCT/JP2007/050232

2.Kato Y, Shao J. et al. Japanese Patent Application No. JP 2008–289146, PCT/JP2009/005573

URL http://www.twocells.com

Life Science

Physical Properties of Food Products and Bio-materials and Their Practical Application

Keywords Melting, Crystallization, Glass Transition, Food Processing, Storage

Kiyoshi KAWAI

Department Graduate School of Biosphere Science
Title Associate Professor / Lecturer
E-mail kawai@hiroshima-u.ac.jp
Field Food Science

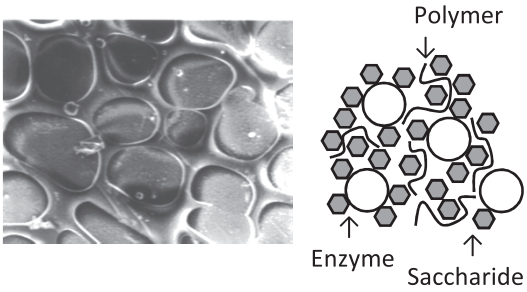
Outline

1. Background

Productivity, storage stability, functionality, and texture of food products and bio-materials are improved by the control of their physical properties.

2. Research Summary

- Storage stability of unstable enzyme was improved by embedding it into saccharide-polymer based glassy matrix.
- High-hydrostatic pressure was used as a novel food processing.
- Melting of crystalline amylopectin was prevented during heat processing. It was found that resistant starch content of the dry starchy food products increased.
- Retrogradation of starch was prevented by adding food substances.



SEM-image of glassy matrix and model of enzyme embedded into there

Enzyme can be embedded into glassy matrix formed by saccharide and polymer during freeze-drying. The saccharide and polymer play a role of solvent of the enzyme and reinforcement of the matrix, respectively.

3. Result

The subjects were achieved in the view of physical properties.

4. For Application

The approach is useful in food and bio industries.

Competitive Advantages

The practical problems in the situation where temperature, pressure, and water content change will be solved. In addition there are possibilities that the quality of current products can be improved.

Patent/Journal/Award

T. Suzuki, N. Hamada-Sato, P. Srirangsan, & K. Kawai. 13/124,562 (USA) and 09820543.8–1223/2351849 (Eur): Reagent kit for measuring freshness, (2011).

URL http://seeds.hiroshima-u.ac.jp/soran_en/e63fc72/ea.html

Life Science

Regulation of Circadian Clock

Keywords Circadian Clock, Sleep Disorder, Lipid Metabolism, Hypertension

Takeshi KAWAMOTO
Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail tkawamo@hiroshima-u.ac.jp
Field Physiology, Biochemistry, Transcription Regulation

Outline

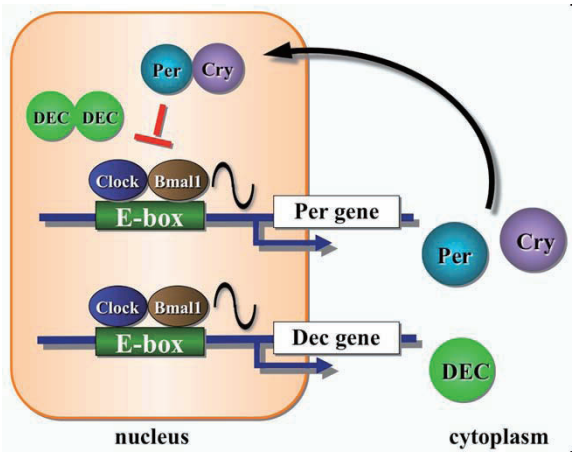
1. Background

Circadian rhythms are one of the most critical biorhythms that are conserved among various species. In mammals, the central pacemaker in the brain regulates diurnal rhythms of various physiological functions such as behavior, feeding, blood pressure, and hormonal secretion, whereas peripheral clocks synchronize various cellular activities, including metabolism and cell cycles, in a tissue-specific manner.

2. Research Summary

The mammalian circadian clock consists of molecular oscillators that depend on a negative transcriptional feedback loop of core clock genes such as Clock, Bmal1, Per, and Cry. Dec1 and Dec2 are also involved in the regulation of the circadian clock. The contribution of Dec1 and Dec2 to the circadian clock is particularly high at some peripheral tissues such as kidney, blood pressure, and adipose tissue.

Circadian clock system



3. Result

Knockdown of Dec1 and Dec2 in cells caused the disruption of circadian rhythms of clock genes, and knockout mice showed the disorder of circadian behavior and gene expression of lipid metabolism-related genes.

4. For Application

The modification of expression of Dec1 and Dec2 or modification of the activity of Dec1 and Dec2 has the possibility to improve the sleep disorders or metabolic syndrome and detect potential disorders.

Competitive Advantages

We isolated Dec1 and Dec2 as key regulators for several physiological function and have a lot of experimental tools such as knockout mice, antibodies, expression vector, and reporter genes.

Patent/Journal/Award

Honma S, Kawamoto T, et al. Dec1 and Dec2 are regulators of the mammalian molecular clock. **Nature**. 2002 419: 841.

Japanese Patent Application No. JP2010–236891

Japanese Patent Application No. JP2011–22172

URL

Life Science

Cell Cryopreservation

Keywords Cell Cryopreservation, Regenerative Medicine, Food Long-term Safekeeping

Toshitsugu KAWATA
Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail tenzan@hiroshima-u.ac.jp
Field Orthodontics

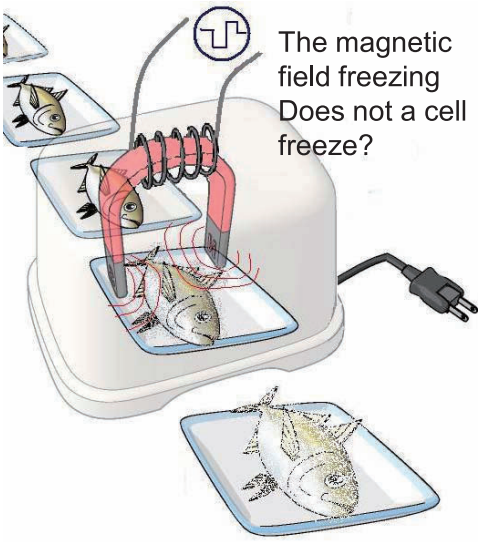
Outline

1. Background
Development of the cryopreservation technology aiming at the long-term safekeeping of the cell.

2. Research Summary
Study for a cell to live after thawing.

3. Result
I completed a magnetic field program freezer.

4. For Application
I can suggest cell long-term safekeeping for food and the medical care.



Competitive Advantages

There are no frozen smell or lyophilization. One can easily experience that a cell lives after thawing.

Patent/Journal/Award

Patent: Hiroshima University six patents in application.

Journal: Kawata T, Abedini S, Kaku M, Koseki H, Kojima S, Sumi H, Motokawa H, Fujita T, Ohtani J, Ohwada N Tanne K. Effects of DMSO (Dimethyl sulfoxide) free cryopreservation with program freezing using a magnetic field on periodontal ligament cells and dental pulp tissues. Biomed Res. 2012. In press

Kaku M, Kojima S, Sumi H, Koseki H, Abedini S, Motokawa M, Fujita T, Ohtani J, Kawata T, Tanne K.Gummy smile and facial profile correction using miniscrew anchorage. Angle Orthod. 2012 Jan; 82(1): 170–7.

Kawata T, Kohno S, Kaku M, Fujita T, Ohtani J, Motokawa M, Tanne K. Expression of vascular endothelial growth factor on neovascularization during experimental tooth movement by magnets. Biomed Res. 22: 248–253. 2011.

Abedini S, Kaku M, Kawata T, Koseki H, Kojima S, Sumi H, Motokawa M, Fujita T, Ohtani J, Ohwada N, Tanne K. Effects of cryopreservation with a newly-developed magnetic field programmed freezer on periodontal ligament cells and pulp tissues. Cryobiology. 2011 Jun; 62(3): 181–7.

Kamada H, Kaku M, Kawata T, Koseki H, Abedini S, Kojima S, Sumi A, Motokawa M, Fujita T, Ohtani J, Ohwada N, Tanne K. In-vitro and in-vivo study of periodontal ligament cryopreserved with a magnetic field. Am J Orthod Dentofacial Orthop. 2011 Dec; 140(6):799–805

Motokawa M, Tsuka N, Kaku M, Kawata T, Fujita T, Ohtani J, Matsuda Y, Terao A, Tanne K. Age-related production of osteoclasts and the changes of serum levels of vascular endothelial growth factor (VEGF) and receptor activator for nuclear factor (NF)-κB ligand (RANKL) in osteopetrotic (op/op) mice. Arch Oral Biol. 2011

Motokawa M, Sasamoto T, Kaku M, Kawata T, Matsuda Y, Terao A, Tanne K. Association between root resorption incident to orthodontic treatment and treatment factors. Eur J Orthod. 2011

Kawata T, Kaku M, Fujita T, Junji Ohtani, Motokawa M, Tanne K. Water molecule movement by a magnetic field in freezing for tooth banking. Biomed Res. 21: 351–354. 2010.

Lee SY, Chiang PC, Tsai YH, Tsai SY, Jeng JH, Kawata T, Huang HM. Effects of cryopreservation of intact teeth on the isolated dental pulp stem cells. J Endod. 3:1336–1340. 2010.

Kaku M, Kamada H, Kawata T, Koseki H, Abedini S, Kojima S, Motokawa M, Fujita T, Ohtani J, Tsuka N, Matsuda Y, Sunagawa H, Hernandes RA, Ohwada N, Tanne K. Cryopreservation of periodontal ligament cells with magnetic field for tooth banking. Cryobiology. 61:73–78. 2010.

Tsutsui K, Kaku M, Motokawa M, Tohma Y, Kawata T, Fujita T, Kohno S, Ohtani J, Tenjoh K, Nakano M, Kamada H, Tanne K. Influences of reduced masticatory sensory input from soft-diet feeding upon spatial memory/learning ability in mice. Biomed Res. 2007 Feb; 28(1): 1–7.

Kaku, M., Kamata, H., Kawata, T., Tai, M., Kohno, S., Motokawa, M., Tohma, Y., Fujita, T., Ohtani, J., Tsuka, N., Ohwada, T. and Tanne, K. : Cryopreservation of PDL cells by use of program freezer with magnetic field for teeth banking. Dentistry in Japan, 43, 82–86, 2007.

Award:
4th Japanese Orthodontic Society International Meeting Distinguished Presentation (2011), Japanese Cleft Palate Association Distiguished Paper (2007), and many more awards received.

URL
Japanese http://www.teethbank.jp/
English http://www.teethbank.jp/english.html

Life Science

Stroma-directed Molecular Targeted Therapy in Gastrointestinal Cancer

Keywords Molecular Targeted Therapy, Metastasis, Cancer-stromal Interaction

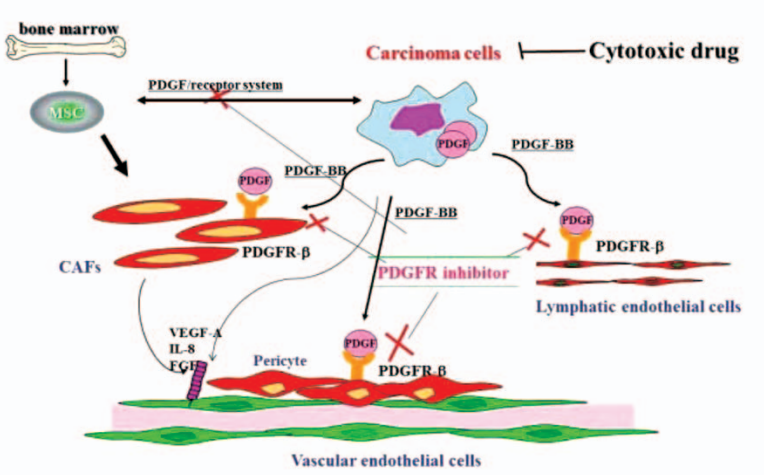
Yasuhiko KITADAI

Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail kitadai@hiroshima-u.ac.jp
Field Gatroenterology, Oncology

Outline

1. Background

Recent studies in tumor biology have shown that tumor growth and metastasis are determined not only by cancer cells, but also by a variety of stromal cells. The stroma constitutes a large part of most solid tumors, and the cancer-stromal cell interaction contributes functionally to tumor growth and metastasis. The aim of the study is to examine whether anti-stromal therapy by PDGF-R inhibitor appears promising as a therapeutic strategy against carcinoma.



2. Research Summary

Tumor stroma contains abundant extracellular matrix and several types of cells, including carcinoma-associated fibroblasts (CAFs), endothelial cells, pericytes and inflammatory cells including macrophages. In gastrointestinal cancer tissues, tumor cells express platelet-derived growth factor (PDGF)-B. Stromal cells, including CAFs, pericytes and lymphatic endothelial cells, express PDGF receptor (PDGFR)-β. Administration of PDGFR tyrosine kinase inhibitor significantly decreases stromal reaction, lymphatic vessel area and pericyte coverage of tumor microvessels. Administration of PDGFR tyrosine kinase inhibitor in combination with cytotoxic chemotherapeutic drug(s) impairs the progressive growth and metastasis of gastric cancer. Activated stroma might serve as a novel therapeutic target in cases of gastric cancer.

3. Result

Treatment with PDGFR inhibitor was shown to significantly decrease the stromal reaction, microvessel area and pericyte coverage of tumor microvessels.
Treatment with PDGFR inhibitor combined with imatinib significantly inhibited tumor growth and lymph node metastases

4. For Application

Modulation of microenvironment may be a new therapeutic strategy for gastrointestinal cancer

Competitive Advantages

Patent/Journal/Award

Sumida, T., Kitadai, Y., et al.: Anti-stromal therapy with imatinib inhibits growth and metastasis of gastric carcinoma in an orthotopic nude mouse model. Int J Cancer 128: 2050–2062, 2011.
Kodama, M., Kitadai, Y., et al.: Expression of platelet-derived growth factor (PDGF)-B and PDGF-receptor beta is associated with lymphatic metastasis in human gastric carcinoma. Cancer Sci 101: 1984–1989, 2010.

URL

Life Science

Development of a Novel Screening and Evaluation System for Useful Peptides by Changing Peptide Utilization Machinery in Yeast

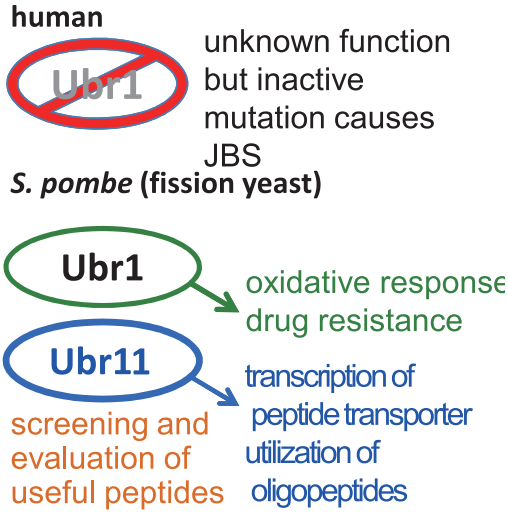
Keywords Ubiquitin, Proteolysis, Yeast, Oligopeptide, Transporter

Kenji KITAMURA
Department Natural Science Center for Basic Research and Development
Title Assistant Professor
E-mail kkita@hiroshima-u.ac.jp
Field Molecular Biology, Applied Microbiology

Outline

1. Background

Some oligopeptides have unique biological action. By modulating regulatory system that controls uptake and utilization of extracellular oligopeptides in yeast, it is possible to develop a novel system for screening and evaluation for new functional peptides or peptidomimetic chemicals. It is also effective way to breed yeast strain harboring new additional valuable traits.



2. Research Summary

Inactive mutation in human Ubr1 ubiquitin ligase gene, which are evolutionarily conserved in eukaryotes, causes recessive disorder Johanson-Blizzard syndrome (**JBS**). To know the physiological role of Ubr1, we have characterized cells lacking *ubr1*-related gene in *S. pombe*, by using yeast as a experimental model organism for human study. The Ubr gene-knock out cells show various abnormalities including altered drug resistance and peptide utilization.

3. Result

Inactivation of *ubr11* gene in *S. pombe* resulted in inability to use extracellular oligopeptides. We isolated mutant that suppresses peptide uptake defect in *ubr11* cells. This mutant is also able to effectively utilize an artificial sweetener aspartate and other modified non-native peptides which are not good nutrients for wild-type cells.

4. For Application

By reconstituting an evaluation system for functional or useful peptides using our yeast mutants, it is possible to breed yeast strain harboring new additional value by potentiating uptake of useful peptides. Our mutant could be also a unique tool to screen new peptides or peptidomimetics exhibiting novel biological action, and explore their action mechanism.

Competitive Advantages

By using our yeast mutants which have altered uptake or metabolism of oligopeptides, or preparing yeast strain lacking its own transporters but expressing only human peptide transporter, it is possible to develop a novel screening system for functional peptides and peptidomimetics, an inexpensive primary assessment system of peptides before using human cells, and a system to explore the mode of action of peptides with genetic techniques of yeasts.

Patent/Journal/Award

Molecular Micribiology (2011) 80, p739-
Eukaryotic Cell (2012) 11, p312-

URL

Life Science

Identification of Mesenchymal Stem Cell Gene Markers for Quality Control

Keywords Mesenchymal Stem Cell, Biomarker, Serum Free Culture Medium

Kazuko KITAYAMA

Department Institute of Biomedical & Health Sciences
Title Assistant Professor (NEDO Grant Contract)

E-mail kkitayam@hiroshima-u.ac.jp
Field Cellular Biology, Molecular Biology

Outline

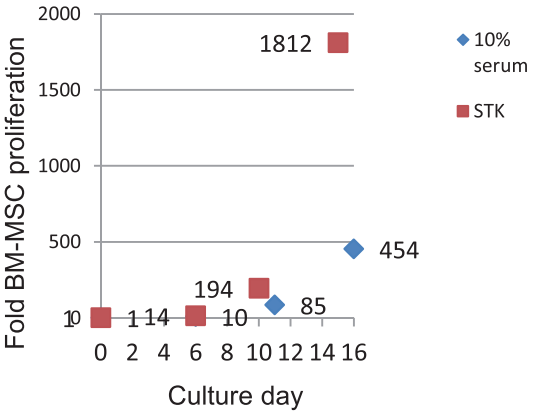
1. Background

We have been developing Bone Marrow Stem cell (BM-MSC) and Synovial MSC (SY-MSC) culture systems to transplant for clinical osteo/chondrocytes regeneration by using serum free culture medium, STK. The STK medium is chemically defined and the MSCs were more proliferative under the STK, so that we aim to confirm the system is safe and highly efficient for clinical use.

2. Research Summary

In order to develop the serum free cultured MSC system, we need to set up biomarkers of cultured MSCs for quality control. We have already examined gene expression profiles of BM-MSCs cultured in serum containing medium and screened the candidate gene markers by examining their gene expression levels of more than 40 human BM-MSC lines. In this on going project, we are searching for candidate gene markers of SY-MSCs in the following 2 steps.

Growth curves of BM-MSCs (P4~P6) cultured in either 10% serum containing medium or serum free medium (STK).



Step 1) Set up gene markers of SY-MSC cultured in serum containing medium. A) By examining mRNA expression of gene markers set up in the BM-MSCs cultured in serum containing medium. B) By analyzing gene expression profiles using DNA microarray technique.
Step 2) Set up gene markers of SY-MSC cultured in STK medium by the methods shown above.

3. Result

We picked up several of candidate gene markers from SY-MSCs cultured in serum containing medium. We prepared test samples of BM-MSCs, SY-MSCs, and Fibroblasts to test the candidate marker gene expression. Availability of the serum medium cultured BM-MSC markers in SY-MSCs is still tested. We are also collecting additional test SY-MSC samples from donated synovial tissues for future examination.

4. For Application

Tissue regeneration therapy.

Competitive Advantages

Quality of MSCs were examined by detecting combination of cell surface antigens of MSCs using flowcytometry technique conventionally. However, this methods needs many numbers of MSCs to judge the cell quality. Our strategy has advantages in the following points,
1) We just need less number of the cells for quality control. 2) we can set up the gene markers that ensure the SY-MSC quality based on characteristics of the MSCs, such as undifferentiated status/stemness, non contamination of other cell source, non malignancy, etc.

Patent/Journal/Award

Kato, Y., et., al. Hiroshima Shi-shi, 39, p1~p8, 2011.

URL

Life Science

Search for Novel Key Role Molecule of Pain Signaling

Keywords Neuropathic Pain

Tomoya KITAYAMA

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail kitayama@hiroshima-u.ac.jp

Field Neuroscience, Pharmacology

Outline

1. Background

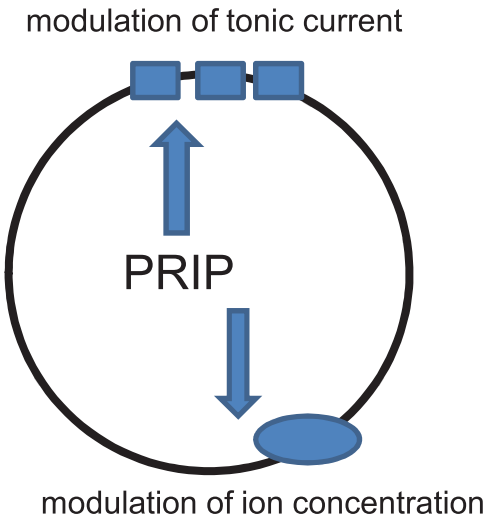
Analysis of onset mechanism of neuropathic pain

2. Research Summary

Many molecules mediate development and / or sustention mechanism of neuropathic pain. Our purpose is to identify essential signals for the onset of neuropathic pain. To achieve this goal, the analysis of regulator molecule of neuropathic pain is developed. Moreover, We search for novel therapeutic target molecule of neuropathic pain.

3. Result

We demonstrated that PLC related catalytically inactive protein (PRIP) regulated pain signaling.



4. For Application

To achieve the goal, the analysis of PRIP function and the search for modulator of PRIP should be done.

Competitive Advantages

Our study is novelty and seminal, because PRIP was identified novel inositol 1, 4, 5-trisphosphate binding protein by our professor KANEMASTU et al.

Patent/Journal/Award

URL

Life Science

Construction of the Tongue Pressure and the Lips Pressure Counting System Using a Super-thin Pressure Sensor, and its Clinical Application

Keywords Tongue-lip Pressure, Masticatory Function

Myongsun KOH

Department Hiroshima University Hospital

Title Assistant Professor

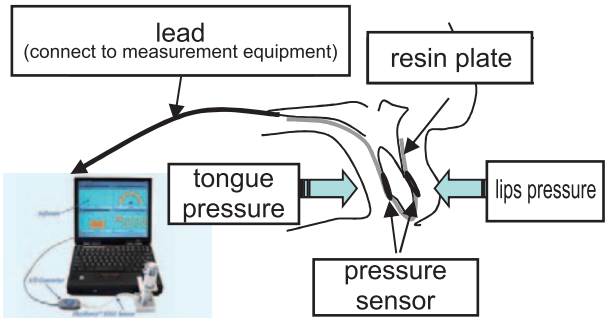
E-mail k1008@hiroshima-u.ac.jp

Field Orthodontic and Pediatric Dentistry

Outline

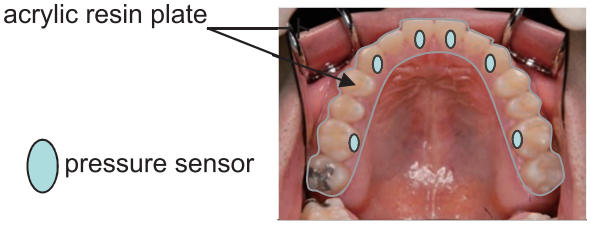
1. Background

Lip and tongue pressure play an important role in the field of masticatory function. These days, the necessity of preventing aspiration pneumonitis by changing a meal form understanding the lips and tongue pressure which decreased in connection with advanced age is also preached. Thus, the necessity of evaluating the pressure of a tongue or lips and the degree of strain objective not from subjective and qualitative evaluation but from a scientific position is searched widely, The database construction of the lips pressure and tongue pressure and establishment of the simple measurement method are considered to be applicable not only to a dentistry clinical but to various fields.



2. Research Summary

The aims of this study was to establish the simple measurement method which used the pressure sensor and to construct the index which faces dietary education by building the database of the tongue and lip pressure in an individuality neutral occlusion.



3. Result

4. For Application

It is assumed that this system is needed in all the fields (geriatric dentistry, denture, orthodontics, oral rehabilitation, etc.) aiming at an improvement of occlusion and eating. It can be used clinically by changing a hard acrylics resin plate into the plastic sheeting which can operate, since it is thought that it is higher-precision by using the leadless sensor, and construction of a simple counting system is possible. Development of these measurement apparatus and material is expected to be done at companies.

Competitive Advantages

By the conventional measuring method, in the balloon of a tongue pressure probe, although a patient carries out upbringing measurement to a palate wrinkles wall with the maximum tongue pressure, operation is complicated and a patient's action is not stabilized. Moreover, measurement of lips pressure required for predation and an eating cannot be performed. The tongue and lips pressure measurement at rest and ingestion and swallowing are attained without barring natural operation by using the system of this research.

Patent/Journal/Award

URL

Life Science

Long-term Effects of Poison Gas Exposure on the Incidence of Respiratory Diseases

Keywords Inhalation Exposure, Mustard Gas, Lung Cancer, Chronic Bronchitis

Nobuoki KOHNO

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail nokohno@hiroshima-u.ac.jp

Field Pulmonary Medicine

Outline

1. Background

On Okuno-jima, a small island in Hiroshima Prefeture in Japan, a poison gas factory established by the Japanese army was in operation from 1929 to 1945. Mustard gas was the main product, but lewisite (chlorvinylarsine), diphenylcyanarsine, hydrocyanic acid, phosgene, and chloracetophenone were also produced. Production of the poison gases reached its peak in 1937. Because the supply of protective clothing was limited, exposure to the gases was substantial. Today the former workers employed in the poison gas factory are known to suffer from a variety of severe residual damages, although long-term effects of poison gases on various types of respiratory diseases are unclear.

2. Research Summary

Since 1952 and for more than 50 years, we have investigated and provided health care to the former workers employed in the poison gas factory in Okuno-jima.

3. Result

We previously reported that a number of former workers were suffered from acute injuries, including erosion and bullae formation in the skin, as well as chronic bronchitis and lung cancer after a period of latency. In 1968, Wada et al reported a high incidence of respiratory neoplasia among the former poison gas factory workers. In 1970, Nishimoto et al reported that recurrent exposure to poison gas can result in chronic bronchitis and irreversible airway obstruction. Recently, we also demonstrated the 1st results of chemical carcinogenesis by mustard gas epidemiologically proven that one year of exposure in subjects ≤18 or >18 years old at first exposure shifted the age scale down by 4.9 years and 3.3 years, respectively. On the basis of the long-term follow-up of former workers in the poisonous gas factory, we concluded that sulfur mustard decreased the age at which people were at risk of developing lung cancer and that the effect declined with aging.

4. For Application

In the Iran-Iraq conflict between 1980 and 1988, approximately 45,000 military and civilian casualties were associated with sulfur mustard gas, and not only acute consequences after inhalation but also a series of chronic destructive pulmonary sequelae have been reported. We hope that our investigations will be beneficial for the future health care of all persons exposed to these chemical agents.

Competitive Advantages

To the best knowledge, this is the first study to the long-term effect of poison gas exposure on the incidence of various types of respiratory diseases.

Patent/Journal/Award

(1) Research on the Aftereffects and Prognosis of Poison Gas Injuries received the 63th Public Health Award, 2011.

(2) Doi M, Hattori N, Yokoyama A, Onari Y, Kanehara M, Masuda K, Tonda T, Ohtaki M, Kohno N. Effect of mustard gas exposure on incidence of lung cancer: A longitudinal study. Am J Epidemiol 2011 Mar 15;173(6):659–66. Epub 2011 Feb 18

URL http://home.hiroshima-u.ac.jp/naika2/en/respiratory/kl-6/index.html

Life Science

Utility of KL-6/MUC1 in the Clinical Management of Interstitial Lung Diseases

Keywords KL-6, MUC1, Serum Biomarker, Interstitial Lung Disease

Nobuoki KOHNO

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail nokohno@hiroshima-u.ac.jp

Field Pulmonary Medicine

Outline

1. Background

Interstitial lung diseases (ILDs) are a diverse group of pulmonary disorders characterized by various patterns of inflammation and fibrosis in the interstitium of the lung. The identification of serum biomarkers for ILDs would greatly improve current diagnostic methods. To date, various serum biomarkers have been tested for their use in ILDs. Among these, biomarkers derived from type II pneumocytes have been of particular interest, because ILDs show a common pathophysiological development, i.e., type II pneumocyte injury or remodeling. The most widely used biomarkers for ILDs derived from type II pneumocytes are Krebs von den Lungen-6 (KL-6) and 2 surfactant proteins, SP-A and SP-D.

2. Research Summary

A murine IgG1 monoclonal antibody (mAb) was developed to recognize a sialylated sugar chain, designated as KL-6, by immunizing a mouse with the human lung adenocarcinoma cell line VMRC-LCR. KL-6 is now classified as a human MUC1 mucin protein, and regenerating type II pneumocytes are the primary cellular source of KL-6/MUC1 in the affected lungs of patients with ILD. A cooperative study on KL-6 as a serum biomarker was initiated with the diagnostic division of Eidia Co., Ltd. (Tokyo, Japan) in 1992. The findings of this study led to the development of an enzyme-linked immunosorbent assay (ELISA) that enabled the determination of the absolute amount of KL-6 in samples collected in clinical practice. KL-6 has been approved by Japan's Health Insurance Program as a diagnostic marker for ILDs since 1999, and KL-6 levels are examined in more than 2,000,000 samples per year in Japan.

3. Result

Based on the results from a number of reports investigating KL-6/MUC1, the serum levels of KL-6/MUC1 are thought to be useful for (1) detecting the presence of disease, (2) evaluating disease activity, and (3) predicting outcomes in various types of ILDs.

4. For Application

In Japan, KL-6/MUC1 has been used in clinical practice for more than 10 years; however, evidence from clinical trials validating the clinical efficacy of KL-6/MUC1 remains limited. In addition, we are aware of ethnic differences in the prevalence of pulmonary diseases such as drug induced-ILDs and cystic fibrosis and in the serum levels of KL-6/MUC1. In order to establish KL-6/MUC1 as an internationally useful serum biomarker, further prospective and international studies to determine the clinical efficacy of KL-6/MUC1 in the management of patients with ILDs are necessary.

Competitive Advantages

Because the measurement of serum KL-6/MUC1 levels is rapid, inexpensive, reproducible, less invasive, and easier to perform than surgical lung biopsy, high-resolution computed tomography, bronchoscopic examination, and pulmonary function tests, we believe that this biomarker would provide a significant benefit to the clinical management of patients with ILDs.

Patent/Journal/Award

(1) Japanese Patent No. 2011158: Nobuoki Kohno received patent royalties/licensing fees from Eisai Co., Ltd.

(2) Nobuoki Kohno received the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology in 2011.

URL http://home.hiroshima-u.ac.jp/naika2/en/respiratory/kl-6/index.html

Life Science

Development of Molecular Target Therapy to VEGF and VEGFR against Oral Cancer

Keywords Oral Cancer, VEGF, Molecular Target Therapy

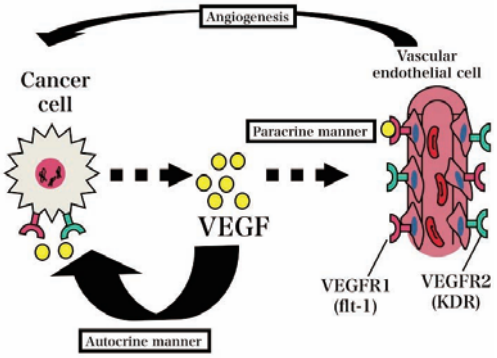
Koichi KOIZUMI

Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail kkoizumi@hiroshima-u.ac.jp
Field Dental Surgery, Clinical Oncology

Outline

1. Background

Cell migration plays a significant role in cancer invasion and metastasis. Our previous studies have shown vascular endothelial growth factor (VEGF) and VEGF receptor 1 (Flt-1) express in oral squamous cell carcinoma (SCC) cells. These finding suggests VEGF-VEGFR system might regulate in autocrine manner as well as angiogenesis in paracrine manner.



2. Research Summary

In this study, we examine the expression of VEGF and VEGFR in oral cancer cells. The participation of VEGF and VEGFR in invasion and metastasis of oral cancer cells is also investigated.

3. Result

Checkerbord analysis showed that VEGF induced Chemotaxitic and Chemokinetic migration in oral cancer cells. The VEGF-induced migration was inhibited by VEGFR tyrosine kinase inhibitor. VEGF induced phosphorilation of Akt. PI3 kinase inhibitor blocks the VEGF-induced phosphorilation of PI3/Akt kinase cascade, and suppressed VEGF-induced motility of oral cancer cells. These findings suggest that migration of oral cancer cells is regulated with VEGF-induced activation of PI3/Akt kinase cascade.

4. For Application

I think that development of molecular target therapy to VEGF and VEGFR against oral cancer leads to be a new clinical therapy.

Competitive Advantages

I examine the autocrine manner of VEGF-VEGFR system, not paracrine manner (for example angiogenesis)

Patent/Journal/Award

Fanctional analysis of VEGF-VEGFR system in human melanoma cells: Jpn. J. Tissue Cult. Dent. Res. 14(1) 39–40,2005

URL

Life Science

Establishment of Standards for Dental Implant Removal with Resorption of Surrounding Bone

Keywords Static, Implant, Osseointegration

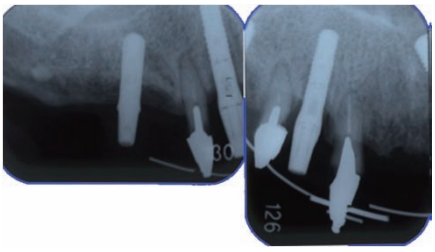
Katsunori KORETAKE

Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail katsu@hiroshima-u.ac.jp
Field Prosthetic Dentistry

Outline

1. Background

Many of implant studies aim to improve speed of osseointegration and to maintain it for a longer period. While implant treatment becomes popular, it is expected that there will be more failure implants. On the other hand, the evidence of standards for removal is yet to be identified.



X-ray picture of implant with bone resorption

2. Research Summary

The necessity to remove implant or not, is verified in animal tests according to the resorption of surrounding bones of implants.
Examined prognosis of implant, by identifying whether or not the influence of dynamic load on the implant with bone resorption is to continue after the removal of load.

Implant with bone resorption

3. Result

Part of relationship between bone resorption and supporting ability of dynamic load was clarified.

4. For Application

For clinical application, further accumulation of animal test results and clinical data is required.

Competitive Advantages

By tackling issues ahead we may face in the near future, measures and direction of research before solution can be proposed

Patent/Journal/Award

URL

Life Science

Molecular Cloning and Analysis of a Biosynthetic Gene Cluster for the Anti-tubercular Agent D-cycloserine

Keywords Anti-tubercular Agent, D-Cycloserine, Biosynthesis, Molecular Cloning, *Streptomyces*

Takanori KUMAGAI

Department Institute of Biomedical & Health Sciences

Title Associate Professor

E-mail tkuma@hiroshima-u.ac.jp

Field Pharmaceutics, Biotechnology, Molecular Genetics, Bacteriology

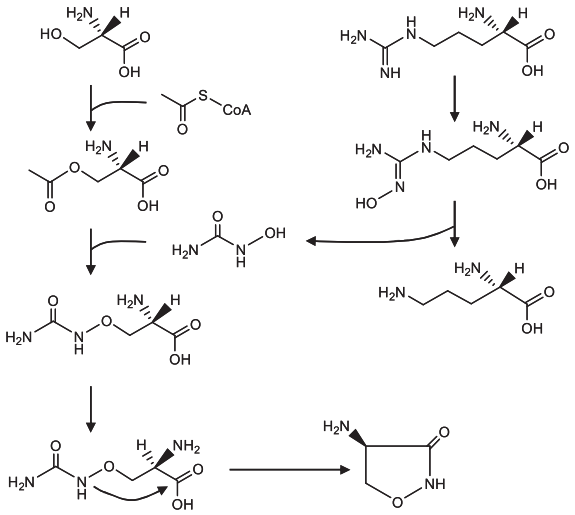
Outline

1. Background

Due to the emergence of multi-drug resistant *Mycobacterium tuberculosis*, it is getting more and more important to discover new anti-tubercular agents.

2. Research Summary

Using a self-resistance gene for D-cycloserine as a probe DNA, a D-cycloserine biosynthetic gene cluster was cloned from a D-cycloserine-producing *Streptomyces lavendulae* ATCC11924. In addition, by using gene disruption methods, function of the genes involved in the cluster was analyzed.



3. Result

A gene cluster that consists of 10 genes including two self-resistance genes was cloned from *S. lavendulae* ATCC11924. Heterologous expression of the cluster in *S. lividans* revealed that the cluster is responsible for D-cycloserine biosynthesis. Based on the sequence information of the gene products in the cluster, a putative biosynthetic pathway for D-cycloserine was proposed. By using gene disruption methods, genes necessary for the biosynthesis of D-cycloserine were clarified.

4. For Application

Enzymes that catalyze unique reactions are found in the biosynthetic pathway of D-cycloserine. By using these enzymes, it may be possible to create new anti-tubercular agents.

Competitive Advantages

This study is the first report identifying a biosynthetic gene cluster for the anti-tubercular agent D-cycloserine.

Patent/Journal/Award

Kumagai *et al.*, Antimicrob. Agents Chemother.

URL http://home.hiroshima-u.ac.jp/sugil/

Life Science

Effects of Statin on Serum Fatty Acid Levels

Keywords Coronary Artery Disease, Fatty Acid

Satoshi KURISU

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail skurisu@hiroshima-u.ac.jp

Field

Outline

1. Background

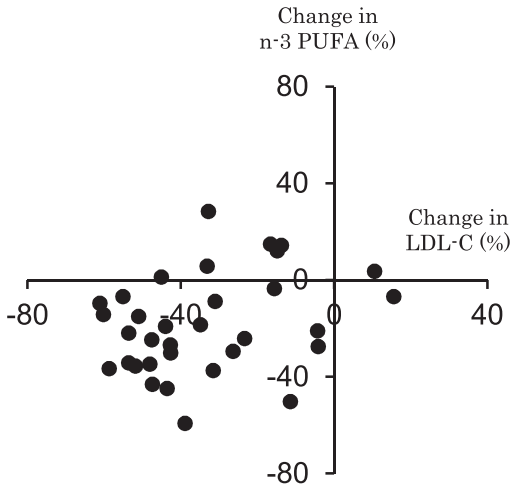
Dyslipidemia, hypertension, diabetes and cigarette smoking are well-recognized as coronary risk factors.

2. Research Summary

There is an increasing evidence that a low ratio of EPA to arachidonic acid (AA) appears as a risk of cardiovascular disease.

3. Result

We demonstrated that statin, which had the effects of low-density lipoprotein cholesterol, reduced the ratio of EPA to AA.



4. For Application

Competitive Advantages

Patent/Journal/Award

URL

Life Science

Human Biomechanics Model and Product Usability Evaluation

Keywords Biomechanics, Human Dynamics, Ergonomics

Yuichi KURITA

Department Graduate School of Engineering

Title Associate Professor

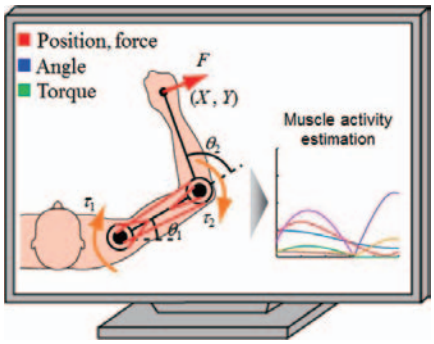
E-mail kurita@bsys.hiroshima-u.ac.jp

Field Perceptual Information Processing, Neurophysiology Muscular Physiology

Outline

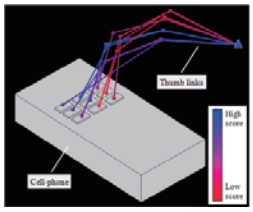
1. Background

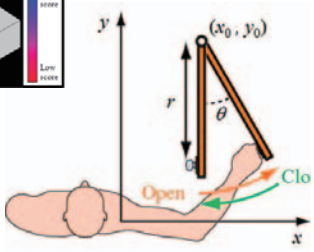
Although a questionnaire survey has been commonly used for the subjective evaluation of usability, the quantitative evaluation of usability and effort in object manipulation would be a useful guideline in product design.



2. Research Summary

We proposed muscle-force-based motion effort evaluation by estimating muscle activity during a motion by means of a musculoskeletal model. The joint torque that produced arm trajectory during a reaching movement was estimated by an inverse dynamics calculation based on human's physical and anatomical parameters. The simulation results showed that the scores of the motion effort based on the joint torque and based on the muscle force have different features. Considering the human's anatomical characteristics, the muscle-force-based motion effort evaluation have the potential to evaluate human's subjective effort.





3. Result

The simulation results showed that the scores of the motion effort based on the joint torque and based on the muscle force have different features. We applied the proposed motion effort index to the design of a door position and a button layout of a mobile.

4. For Application

Considering the human's anatomical characteristics, the muscle-force-based motion effort evaluation have the potential to evaluate human's subjective effort. The proposed muscle-force-based motion effort evaluation method could be applied to the novel quantitative evaluation of the product usability.

Competitive Advantages

Patent/Journal/Award

Yuichi Kurita, Atsutoshi Ikeda, Tadashi Matsumoto, and Tsukasa Ogasawara, "Evaluation of Grasp Efficiency based on Muscle Activity Estimation by Anthropomorphic Robot Fingers," 2011 International Symposium on Micro-Nano Mechatronics and Human Science pp.466–468, Nagoya, Japan, Nov 6–9, 2011

URL http://www.bsys.hiroshima-u.ac.jp/~kurita/index_e.html

Life Science

Tactile and Haptic Models of Humans and Their Applications to Computer Interface

Keywords Computer Interface, Tactile, Haptics, Slip Detection

Yuichi KURITA

Department Graduate School of Engineering

Title Associate Professor

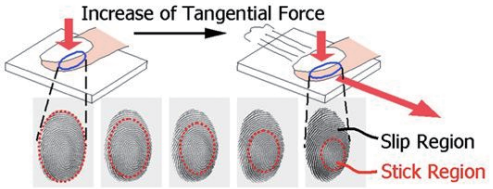
E-mail kurita@bsys.hiroshima-u.ac.jp

Field Perceptual Information Processing, Intelligent Machine, System Engineering

Outline

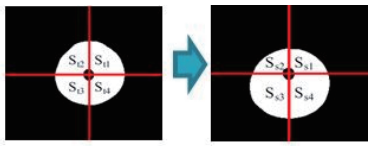
1. Background

Improvement of the computer hardware technology continues to miniaturize notebook computers. PDA (Personal Digital Assistant) and mobile phones have also improved their performance year to year. To operate these compact information devices, input devices should be small and easy to use.

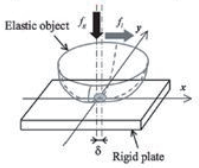


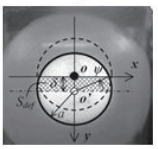
2. Research Summary

The eccentricity is a quantitative index to evaluate the slip condition on a fingertip. The prototype was developed that can capture the contact surface between the fingertip and the transparent plate by an embedded camera in real time.

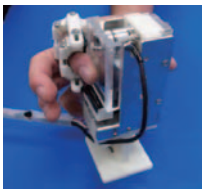


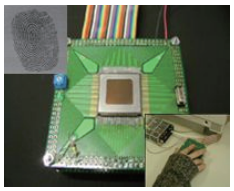
(a) We developed a prototype of the pointing device system. The velocity of the pointer is determined by detecting the center of the fingerprint and calculating the contact area. To confirm the effectiveness of the proposed method, we developed a prototype of the pointing device system. The experimental results showed that an operator can control the pointer with high accuracy.





(b) A weight and friction illusion device that controls the eccentricity of the contact surface was developed. The plate was actuated by a motor to achieve given desired eccentricity by a PID control. The desired eccentricity was obtained by known material parameters, friction coefficient, and force profiles. The grasp and load force profiles of the object with target weight/friction were given by a general force generation model from human measurements. The experimental results showed that the proposed device successfully presented the weight/friction illusions.





3. Result

4. For Application

Competitive Advantages

Patent/Journal/Award

• Yuichi Kurita, Atsutoshi Ikeda, Jun Ueda, and Tsukasa Ogasawara, “A Fingerprint Pointing Device Utilizing the Deformation of the Fingertip during the Incipient Slip,” IEEE Transactions on Robotics, Vol.21, No.5, pp.801–811, 2005.10

URL http://www.bsys.hiroshima-u.ac.jp/~kurita/index_e.html

Life Science

The Morphology and Function of Cells in the Body

Keywords Vitamin A-uptake Cell, Ito Cell, Hepatic Stellate Cell, Mast Cell, Somatostatin Cell, Enterochromaffin Cell

Yoshisuke KUSUMOTO

Department Institute of Biomedical & Health Sciences

Title Associate Professor

E-mail kusumoto@hiroshima-u.ac.jp

Field Physiology(General Anatomy-Histology)

Outline

1. Background

(1) To give a closer view of various cells three-dimensionally which constitute our body and elucidate their physiological movements and activities from it.

(2) To investigate the distribution, localization and cytological features of vitamin A storing cells in our body and elucidate their physiological functions through it.

2. Research Summary

(1) Some of cells in our body were observed using Scanning electron microscopy or reconstructed three-dimensionally with computer-assisted method using serial semithin sections.

(2) Vitamin A uptake cells were investigated ontogenetically and phylogenetically on the distribution in the body, the localization in the organs and the cytological features with light and electron microscopy.

3. Result

(1) The cells in our body change their shape to exhibit well their physiological functions and cope with the microenvironmental alterations at any time.

(2) Vitamin A uptake cells, which take in vitamin A acively and store it in the lipid droplets, are widely distributed In various organs of many species.

4. For Application

Competitive Advantages

I hope that our research results will be any kinds of help or usefulness to elucidate the pathogenesis of certain diseases.

Patent/Journal/Award

Kusumoto et al.; Arch. Histol. Cytol. 40(2), Biomed. Res. 2(5), Arch. Histol. Cytol. 42(4), Arch. Histol. Cytol. 51(3)

URL

Life Science

Evaluation of the Usefulness of a New Electronic Device for Gingival Massage

Keywords Gingivalmassage, Interdental Papilla, Blood Flow

Atsue MATSUMOTO

Department Institute of Biomedical & Health Sciences

Title Associate Professor / Lecturer

E-mail atu@hiroshima-u.ac.jp

Field Social Odontology

Outline

1. Background

Prevention of lesions in teeth and gingiva is important to maintain oral health. Not only plaque control but also maintenance of gingival health is essential to achieve this purpose. For these reasons, efficacy of different gingival massage methods was compared in this study.

Fig.1 new electronic device gingival massager

2. Research Summary

Four different massage methods comprising new electronic gingival massage device, toothbrush, tapping with a finger and scrubbing with a finger were used directly to the gingiva. After 10-second massage to the labial interdental papilla between the maxillary right central incisor and lateral incisor, blood flow was measured with a laser doppler flowmeter.

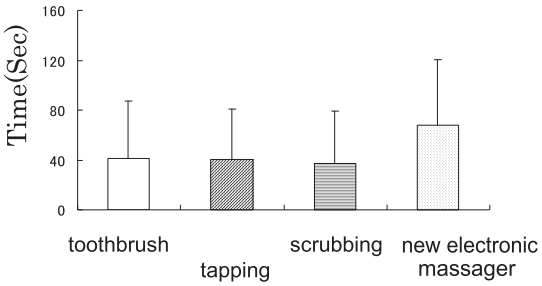


Fig.2 Duration of the increase in gingival blood flow

3. Result

Gingival massage in addition to plaque control is effective for activation of peripheral blood circulation, prevention of periodontal diseases and maintenance of oral health.

The use of the new electric gingival massager made in this study increased blood flow , and duration of the increase in gingival blood flow was longer than others. These results suggest our new device is a better choice for gingival massage in addition to conventional measures.

4. For Application

I hope this new device to be commercially produced by a company. Because the material of the tip must be soft, we need some improvement to make it durable to use longer duration.

Competitive Advantages

Commercially available gingival massage device is only with brush-shaped gum tip. Our new electronic device has a tapered tip, and, as a result, vibration reaches to “col” of gingiva directly. And gingiva does not get injured because the tip movement is vibration, not rotation.

Patent/Journal/Award

Matsumoto Atsue, Journal of Japan Society for Dental Hygiene

URL http://www.hiroshima-u.ac.jp/en/bimes/

Life Science

Discovery of Bioactive Compounds from Okinawa Subtropical Plants

Keywords Natural Product, Subtropical Plant, Okinawa, Cancer, Multidrug Resistance

Katsuyoshi MATSUNAMI

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail matunami@hiroshima-u.ac.jp

Field Natural Product Chemistry

Outline

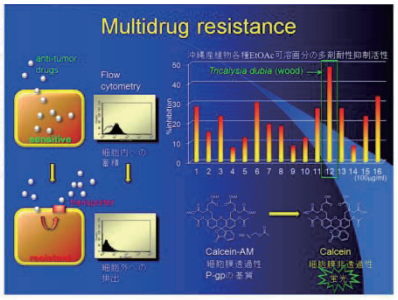
1. Background

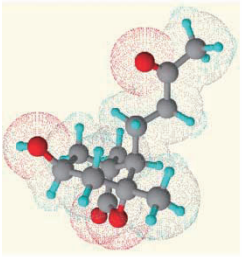
Despite the clinical application of many anticancer agents, the top cause of death is still cancer. Search for new anti-cancer agent is an important issue that must be continuously addressed to continue today.

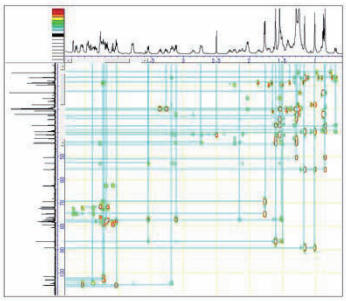
2. Research Summary

The Ryukyu Islands are a rich source of endemic plants and rare species in Japan, providing a valuable resource for natural products chemistry and drug discovery research. Based on the idea of resource localization in recent years, the use of Okinawa subtropical plants is important now and in future years.

From the extracts of several subtropical plants collected in Okinawa, we have successfully isolated the active principles based on the results of bioassays, such as human cancer cell growth and multidrug resistance inhibition assays. Then, the chemical structures of the isolated compounds were investigated in detail by various spectral data and chemical derivatization.







3. Result

Chemical constituent analysis of several plant samples were performed. The active principles were successfully isolated through the combination of several chromatographic procedures. The chemical structure of these compounds were determined in detail.

4. For Application

In the pharmaceutical industry, compounds with new chemical structures and good biological activities have patentability. These compounds may contribute to the development of new drugs.

Competitive Advantages

Although many drugs have been developed by chemical synthetic methods so far, the origin of these compounds are often related to the compounds found from natural resources. Natural products chemistry fundamentally aims to discover the compounds having new chemical structure. Therefore, an important point of patentability is cleared inevitably.

Patent/Journal/Award

The Pharmaceutical Society of Japan, Chugoku-Shikoku Branch Award for Young Scientists (2009)

The Japanese Society of Pharmacognosy Award for Divisional Scientific Contributions (2011)

URL http://home.hiroshima-u.ac.jp/~shoyaku/

Life Science

Structural and Functional Analysis of Three Enone Reductases from *Nicotiana Tabacum*

Keywords *Nicotiana Tabacum*, Enone Reductase

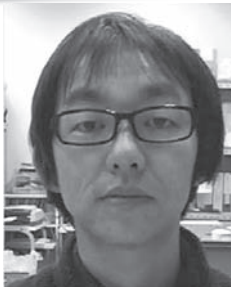
Akihito MATSUSHIMA

Department Natural Science Center for Basic Research and Development

Title Assistant Professor

E-mail masha@hiroshima-u.ac.jp

Field Biochemistry



Outline

1. Background

There are many enzymes involved in secondary metabolism in plant cell. Many of these enzymes have the ability to recognize the stereo structure of substrate to produce chiral products.

In the past, three enone reductases were purified from cultured cells of *Nicotiana tabacum*. (Fig.1) I am analyzing structure and function of these three enone reductases.

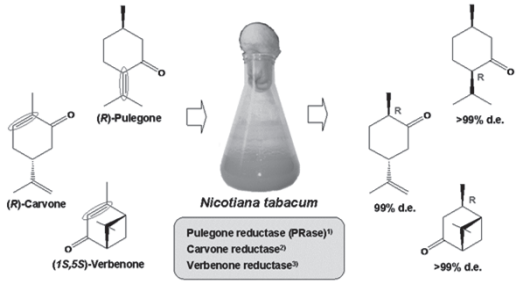


fig. 1

2. Research Summary

The structures of these three enone reductases were analyzed by molecular cloning. The recombinant enone reductase was over expressed in *Escherichia coli* and the function of these recombinant enone reductases was analyzed.

In the past, structure and function of two enone reductases (verbenone reductase and pulegone reductase) was analyzed. Now, I am analyzing the structure and function of carvone reductase.

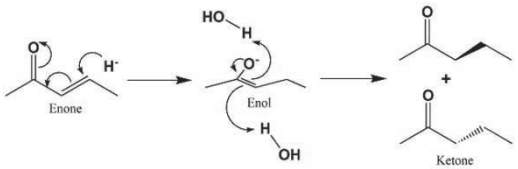


fig. 2

3. Result

In the past, structure and function of two enone reductases was analyzed. The recombinant plegone reductase from *E. coli* does not have stereoselectivity toward pulegone. However, the addition of BSA (Bovine Serum Albumin) improved the stereoselectivity toward pulegone. There may be a factors to control the stereoselectivity of pulegone reductase.

4. For Application

This research may be applied for the production of intermediate of chiral compounds or medicinal chemicals. However, the stereoselectivity of recombinant enzymes was not controlled completely. So, I need to clear the co-factor to controll stereoselectivity of pulegone reductase.

Competitive Advantages

These three enone reductases have the ability to reduce carbon=carbon double bond, however the selectivity of substrate differs from each other. Comparison of these enzymes may offer new insight into the mechanism to controll stereoselectivity or substrate selectivity of enzyme.

Patent/Journal/Award

・Toshifumi Hirata, Akihito Matsushima, Yuya Sato *et al., J. Mol. Cat. B: Enz.*, 59, 158–162 (2009).

・Akihito Matsushima, Yuya Sato, Miki Otsuka *et al., Bioorg. Chem*, 36(1), 23–28 (2008).

URL http://home.hiroshima-u.ac.jp/ricentr/

Life Science

A Colored Frog Strain for Visual Identification of the Genetic Sex of Tadpole

Keywords Sex, Frog, Environmental Disruptor, Mutation

Ikuo MIURA

Department Graduate School of Science
Title Associate Professor
E-mail imiura@hiroshima-u.ac.jp
Field Environmental Biology, Basic Biology

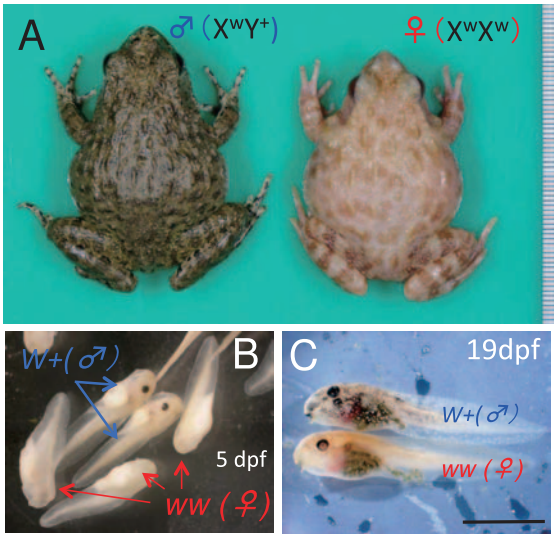
Outline

1. Background

Frog is an excellent animal to detect a chemical substance that is artificially released to water and land environments and disturbs sex of animals, because it is highly sensitive to sex hormones and inhabits both environments during the life. However, identification of the genetic sex during early tadpole stage has been hard and time-consuming.

2. Research Summary

We collected some of color mutants from field and crossed the females with wild-type males, followed by backcrossing the male hybrids to the mutant females. Sex-linkage of the color loci was examined.



3. Result

It was found that a color mutation locus w of Japanese wrinkled frog *Rana rugosa* is X-linked (Fig. A). We established an X^wY^+/X^wX^w strain that could visually identify the genetic sex of tadpoles, black male and white female, from 5 days post fertilization at latest (Fig. B). Also, the frog was found to be highly sensitive to testosterone and estradiol and thus be easily sex reversed in both directions.

4. For Application

This frog strain is applicable to detection of a sex disturbing activity of chemical substance released to environment.

Competitive Advantages

This strain is excellent to detect a chemical substance in the following points: a four-legged animal that inhabits water and land environments during its life, more than 1000 eggs spawned from a female that are genetically homogenous, high sensitivity to sex hormones and sex reversal in both directions, and easy and visual identification of genetic sex during early development.

Patent/Journal/Award

Miura et al. (2011) Sexual Development 5: 250–258.

URL http://home.hiroshima-u.ac.jp/%7eamphibia/miura/first.html

Life Science

Functional Analysis of the Gnathodiaphyseal Dysplasia Gene TMEM16E/GDD1

Keywords Gene, Gene Product, Skeletal Diseases, Muscle Disorders

Kuniko MIZUTA

Department Institute of Biomedical & Health Sciences
Title Assistant Professor

E-mail mihta@hiroshima-u.ac.jp
Field Oral Surgery

Outline

1. Background

We succeeded in identifying a novel gene TMEM16E/GDD1/ANO5 that consists of 22 exons as the gene responsible for gnathodiaphyseal dysplasia(GDD) and proximal limb-girdle muscular dystrophy (LGMD2L) . Since, we have been studying functional analysis of gene product TMEM16E.

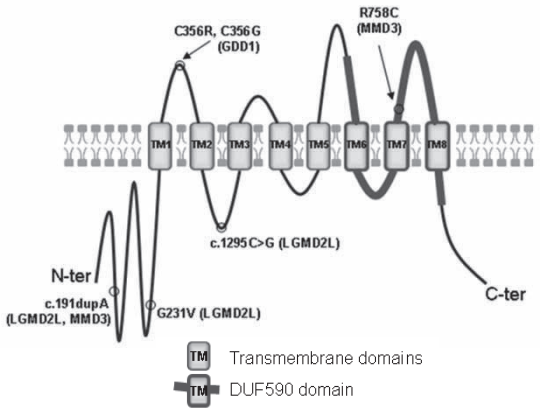
2. Research Summary

As to elucidate the role of the gene and gene product TMEM16E, we examined its intracellular localization and tissue distribution.

3. Result

Biochemical studies indicated that TMEM16E protein is an integral membrane glycoprotein that resides predominantly in intracellular vesicles.

TMEM16E is a member of the newly identified transmembrane 16 (TMEM16) protein family (*TMEM16A~K*). It has been reported that *TMEM16A* and *TMEM16B* play a role as a calcium-activated chloride channel. However TMEM16E gene product showed no chloride channel activity, it can have different functions as expected. Furthermore, TMEM16E protein showed a significant protein instability by comparison with TMEM16A protein. In addition, TMEM16E protein was found to be stabilized specifically in muscle cells.



The prediction of secondary structure and gene product TMEM16E.
And the relative position of the mutation identified at LGMD2, MMD3,GDD.

4. For Application

TMEM16E gene was also identified as a disease of the muscular dystrophy gene not only in bone disease. Therefore, to elucidate its function, there is a possibility to contribute the establishment of understanding of the pathophysiology and treatment of osteoporosis and various muscle diseases.

Competitive Advantages

GDD is the concept of disease which is defined for the first time in Japan, and our research group has identified the causative gene. In this study, we are unrivaled at present.

Patent/Journal/Award

- Bolduc V, Marlow G, Boycott KM, Saleki K, Inoue H, Kroon J, Itakura M, Robitaille Y, Parent L, Baas F, **Mizuta K,** Kamata N, Richard I, Linssen WH, Mahjneh I, de Visser M, Bashir R, Brais B: Recessive mutations in the putative calcium-activated chloride channel Anoctamin 5 cause proximal LGMD2L and distal MMD3 muscular dystrophies. *Am J Hum Genet*. 2010 Feb 12; 86(2): 213–21.
- **Mizuta K,** Tsutsumi S, Inoue H, Sakamoto Y, Miyatake K, Miyawaki K, Noji S, Kamata N, Itakura M: Molecular characterization of GDD1/TMEM16E, the gene product responsible for autosomal dominant gnathodiaphyseal dysplasia. *Biochem Biophys Res Commun*. 357: 123–32, 2007.
- Tsutsumi S, Inoue H, Sakamoto Y, **Mizuta K,** Kamata N, Itakura M: Molecular cloning and characterization of the murine gnathodiaphyseal dysplasia gene GDD1. *Biochem Biophys Res Commun*. 331: 1099–106, 2005.

URL

Life Science

Development of a Novel Kind of Radioprotectors That Inhibit Radiation-induced Cell Death

Keywords Radioprotector, Cell Death, Apoptosis, p53, Sodium Orthovanadate

Akinori MORITA

Department Research Institute for Radiation Biology and Medicine

Title Assistant Professor

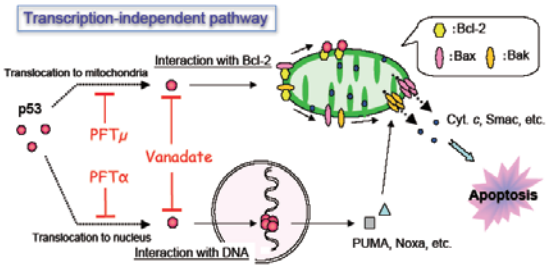
E-mail morita@hiroshima-u.ac.jp

Field Radiobiology, Radiation Medicine

Outline

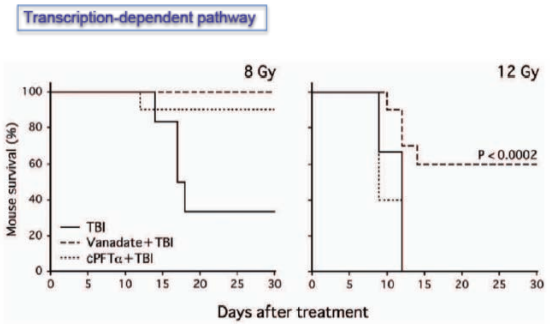
1. Background

Radiation therapy and chemotherapy occasionally cause some adverse side effects by inducing DNA damage-induced apoptosis in normal tissues. These side effects frequently restrict their use. Since nearly half of cancers carry the impaired p53 functions, p53 inhibitors are expected to exert selective protection of normal tissues in cancer therapy, and as well to be useful in cases of emergency exposure accidents.



2. Research Summary

In this study, radiation-induced apoptosis in some cell lines and acute radiation syndrome in total-body irradiated mice were used as models for lethal radiation injury to evaluate the radioprotective p53-inhibitory activities of candidate compounds.



3. Result

We have demonstrated that sodium orthovanadate (vanadate) is the first inhibitor that can protect death from radiation-induced gastrointestinal syndrome in mice by blocking both transcription-dependent and transcription-independent p53 apoptotic pathways. We are currently developing a novel kind of radioprotectors that target the zinc binding site of p53.

4. For Application

The only radioprotective drug approved by FDA for use in radiation therapy is amifostine, which was sold under the trade name “Ethyol.” However, significant side effects related to amifostine include nausea, vomiting, and hypotension, which restrict its use. Although vanadate has a comparable radioprotective efficacy and a particular mitigating activity that is still effective even after irradiation, we observed an acute lethal toxicity when administered by three-fold higher doses. Therefore, a novel, less toxic compound capable of suppressing both p53 pathways may serve as a therapeutic inhibitor of p53.

Competitive Advantages

Recently, some radioprotectors that inhibit apoptosis by some means have been introduced. Among these inhibitors, p53 inhibitors have a good advantage for the selective protection of normal tissues.

Patent/Journal/Award

Cancer Res. 70, 257–265, 2010; Cell Death Differ. 13, 499–511, 2006.

Young Scientist Award of the 53rd Annual Meeting of the Japan Radiation Research Society

Best Poster Award of the 50th Annual Meeting of the Japan Radiation Research Society

URL http://www.nirs.go.jp/information/press/2009/02_12.shtml

Life Science

Development of Chronic Disease Management Programs and the Care Delivery System

Keywords Chronic Disease, Disease Management, Educational Program & Materials

Michiko MORIYAMA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail morimich@hiroshima-u.ac.jp

Field Clinical Nursing (Chronic Care Nursing & Family Nursing)

Outline

1. Background

Although the disease structure has shifted from communicable to non-communicable diseases, the medical care delivery system in Japan has retained the same structure with an emphasis on in-hospital treatment in the acute stage, resulting in much inefficiency and inefficacy. Chronic diseases require long-term self-management and co-management with medical professionals, which further calls for a patient management program, educational materials and a new system which can provide both.

2. Research Summary

2.1. Educational materials were developed and clinical trials were conducted in terms of diabetes, diabetic nephropathy, CKD, COPD, CVA, MI, CHF, and cancer (symptom management).
2.2. Community organization is carried out for the purpose of activating a community and improving health indicators with an emphasis on the prevention of the elderly's withdrawal and on the chronic disease management. Also, a program is being developed to improve the elderly's health indicators.
2.3. In order to effectively provide these services, a new system is being implemented in residential blocks with ageing populations in urban cities, municipalities, rural areas and islands and areas affected by disasters.

3. Result

In terms of 2.1., the physiological and psychological-social indicators and QOL of the intervention group improved with statistical significance compared with the control group, manifesting significantly less re-hospitalization and recurrence of the disease, resulting in improved effects.
In terms of 2.2. and 2.3., the experiments are currently in session.

The COPD program & the kit

The diabetic nephropathy program & the kit

4. For Application

A university-based venture corporation was founded in December, 2010, which is called DPP Health Partners, Inc. and is providing services to the medical insurers (municipalities [National Health Insurance]), the National Health Insurance Association, health insurance unions of corporate businesses and individuals. Receiving subsidies from the government, we are also building a new network of chronic disease management for the areas afflicted by the disasters. In order to construct a new chronic disease management system for the entire country, we are in need of grants from a large number of companies in terms of developing IT systems, network related technologies, and educational materials.

Competitive Advantages

There are no comparable studies or businesses; even if they do exist, they are limited to the area of primary prevention (specified health instruction) or to specific diseases, indicating that there are practically no organizations that widely provide chronic disease management programs and a research-based system. Also, the present project provides a program to train specialized nurses for chronic disease and provides excellent nurse education and research as a set. Herein lie its advantages.

Patent/Journal/Award

Otus, Moriyama.(2011). Effectiveness of an educational self-management program for outpatients with chronic heart failure. *Japan Journal of Nursing Science, 8*, 140–152. Kazawa, Moriyama.(2011).
Self-management educational support for patients with diabetic nephropathy who has difficulty of behavior change. *Journal of Japanese Society for Chronic Illnesses and Conditions Nursing, 5(2)*, 48–52. Moriyama et al. (2009). Efficacy of a self-management education program for people with type 2 diabetes: Results of a 12 month trial. *Japan Journal of Nursing Science, 6(1)*:51–63. (Excellent Paper Award from Japan Academy of Nursing Science)

URL DPP Health Partners, Inc. http://dpphp.jp/, http://home.hiroshima-u.ac.jp/seijin/index.html

Life Science

Application of Manufacturing Systems Technology to Dentistry

Keywords Bio-medical Engineering, CAD/CAM/RP, Simulation, Production Management

Takeshi MURAYAMA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail murayatk@hiroshima-u.ac.jp

Field Human-medical Engineering, Dentistry, Informatics, Mechanical Engineering

Outline

1. Background

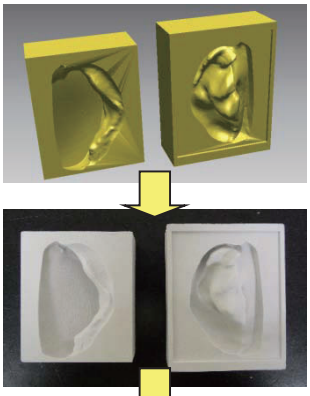
Various things are fabricated for medical treatment and restoration in medical and dental fields. The fabrication is not efficient since it is performed manually.

2. Research Summary

To fabricate them efficiently, we developed a method using manufacturing systems technology, especially CAD (Computer-aided Design)/CAM (Computer-aided Manufacturing) and 3-D printer techniques.

3. Result

We showed that artificial fingers and auricles were able to be fabricated, based on the developed method.



3-D model of a mold

Mold made by 3-D printer

Artificial auricle made by pouring silicone resin into the mold

4. For Application

We need to examine a method to reduce the fabrication time, to put our method to practical use.

Competitive Advantages

When the quality of an artificial body part has deteriorated because of long time usage, we need to fabricate the same artificial body part again. In such a case, our method is very effective. Namely, our method enables us to fabricate the same artificial body part easily by using the 3-d model stored in a computer.

Patent/Journal/Award

URL

Life Science

Development of Protamine as a Protective Agent against Drug-induced Nephrotoxicity

Keywords Polypeptide, Drug-induced Nephrotoxicity, Aminoglycoside Antibiotics

Junya NAGAI

Department Institute of Biomedical & Health Sciences

Title Associate Professor

E-mail jnagai@hiroshima-u.ac.jp

Field Pharmaceutical Sciences

Outline

1. Background

In clinical situations, administration of some medicines is often interrupted by their adverse effects or is avoided because of concern about such possible side effects. Therefore, development of drugs which can be administered to patients more efficiently and safely is required.

2. Research Summary

Aminoglycoside antibiotics (AG) such as gentamicin (GM) are widely used for treatment of serious Gram-negative infectious disease. However, serious complications like nephrotoxicity and ototoxicity are dose-limiting factors in the use of AG. It is considered that such adverse effects are due to specific accumulation of AG in the renal proximal tubular cells and inner ear hair cells. Several endocytic receptors and cation channels are reported to be involved in specific accumulation of AG in the epithelial cells.

In this study, we examined whether or not protamine, a cationic polypeptide, is useful for a protective agent against GM-induced nephrotoxicity.

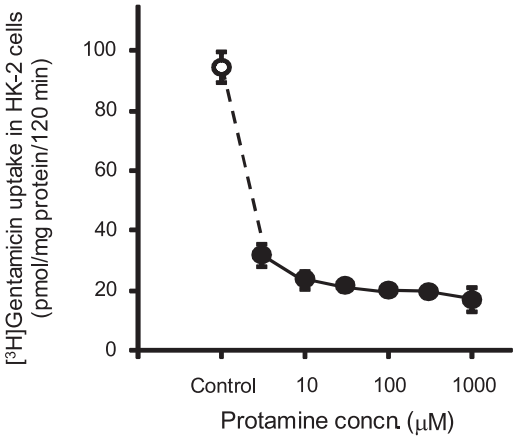


Fig. Effect of protamine on [^{3}H]gentamicin uptake in HK-2 human kidney proximal tubular cell line.

3. Result

We examined the effect of protamine on [^{3}H]gentamicin ([^{3}H]GM) uptake in HK-2 human renal proximal tubular cell line. Protamine inhibited [^{3}H]GM uptake in a concentration-dependent manner with an IC_{50} value of 5.9 μM (Fig.). The IC_{50} value for protamine was lower than some other inhibitors which we found previously.

4. For Application

Protamine is already used as a food additive or a medicine. Therefore, food or pharmaceutical companies might have an interest in our results described above. The challenge for this study is to decrease the dose at which protamine reduces AG accumulation in the kidney under in vivo conditions though protamine very potently inhibits AG uptake under in vitro conditions.

Competitive Advantages

Many approaches to ameliorate AG-induced nephrotoxicity have been so far reported. However, most of such previous approaches have focused on the protective effects on events occurring after AG are internalized into cells. In contrast, our approach is based on the protective effect by blocking the uptake of AG in the cells, which could completely prevent AG-induced nephrotoxicity.

Patent/Journal/Award

Nagai, J. and Takano, M. (2010) Expert Opin. Drug Metab. Toxicol. 6, 1125–1138.

URL

Life Science

Modification of Plant Fundamental Metabolism by the Use of nMat1 Gene

Keywords Plant Biotechnology, Metabolism, Mitochondria

Naoki NAKAGAWA

Department Graduate School of Biosphere Science

Title Assistant Professor

E-mail naka@hiroshima-u.ac.jp

Field Plant Physiology and Molecular Biology

Outline

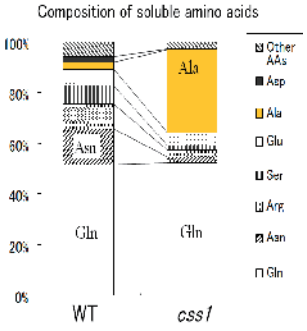
1. Background

The production of plant valuable metabolites depends on the efficient fundamental carbon and nitrogen metabolisms. Mitochondria play indispensable roles in the fundamental metabolism. Recently, many important genes that regulate mitochondrial RNA metabolism have been identified.

2. Research Summary

We have identified a nuclear gene (nMat1) that was indispensable in the efficient splicing of plant mitochondrial mRNA. A mutation of this gene (css1) widely influenced productivity of many kinds of valuable plant metabolites, such as amino acids, lipids and anthocyanin. The influences of the malfunction of this gene were prominent at the early phase of plant growth.

Amino acids

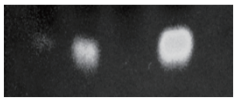


Anthocyanin

Suc 2%

WT css1

Triacylglycerol



Glc 1% Glc 3%

WT css1 WT css1

3. Result

Our studies indicated that plant fundamental metabolisms can be widely modified by the repression nMat1 gene function.

4. For Application

Our finding can be applied to improve productivity of plant valuable metabolites.

Competitive Advantages

The repression nMat1 gene function can be achieved by natural or artificial mutation. Therefore, there is no need to use transgenic technology.

Patent/Journal/Award

Plant Cell Physiology 47(6): 772–783 (2006)

URL http://home.hiroshima-u.ac.jp/naka/wiki/wiki.cgi?FrontPage

Life Science

Biomechanical Function of Anterior Cruciate Ligament Remnants

Keywords Anterior Cruciate Ligament, Partial Rupture, ACL Remnant

Atsuo NAKAMAE

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail nakamae@hiroshima-u.ac.jp

Field Clinical Medicine; Orthopaedic Surgery

Outline

1. Background

The present study aimed to evaluate the biomechanical function of anterior cruciate ligament (ACL) remnants in antero-posterior and rotational knee stability in patients with a complete ACL injury.

2. Research Summary

ACL remnants were classified into 5 morphological patterns (Group 1: bridging the posterior cruciate ligament (PCL) and tibia, Group 2: bridging between the intercondylar notch and tibia, Group 3: partial rupture of the posterolateral bundle, Group 4: partial rupture of the anteromedial bundle, Group 5: no substantial ACL remnants). The decision of whether the remaining bundle represents partial rupture or complete rupture of the ACL was made on the basis of physical, MRI, and arthroscopic findings in a comprehensive manner. Patients in Groups 1 (n=18) and 2 (n=12) underwent intraoperative arthrometry with a navigation system before and immediately after resection of the ACL remnant. Effects of chronicity (duration between injury and surgery) and ACL remnant pattern on changes in knee laxity after debridement of the ACL remnant were investigated.

3. Result

Chronicity had a significant effect on changes in the antero-posterior knee laxity evaluated at 30° knee flexion following resection of the ACL remnant (chronicity ≤ 1 year, change in laxity = 2.22 mm; chronicity > 1 year, change in laxity = 0.17 mm). Chronicity did not influence changes in rotational knee stability after resection of the remnant. There were no significant differences between Groups 1 and 2 with regard to any of the evaluated changes in knee stability.

4. For Application

The harmless device for evaluation of knee kinematics is desirable.

Competitive Advantages

In Groups 1 and 2, ACL remnants contributed to antero-posterior knee stability evaluated at 30° knee flexion for up to 1 year after injury, beyond which this biomechanical function was lost. Chronicity and remnant pattern did not influence changes in rotational knee stability after resection of the remnant.

Patent/Journal/Award

Arthroscopy. 2010 Dec; 26(12): 1577–85. Nakamae A, Ochi M, Deie M, Adachi N, et al.

URL

Life Science

Effects of Knee Immobilization on Regeneration of the Semitendinosus Tendon and on the Proximal Shift of the Semitendinosus Muscle-tendon Junction after Hamstring Harvesting for Anterior Cruciate Ligament Reconstruction: Evaluation Using Three-dimensional Computed Tomography

Keywords Semitendinosus Tendon, Regeneration, 3D CT

Atsuo NAKAMAE

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail nakamae@hiroshima-u.ac.jp

Field Clinical Medicine; Orthopaedic Surgery

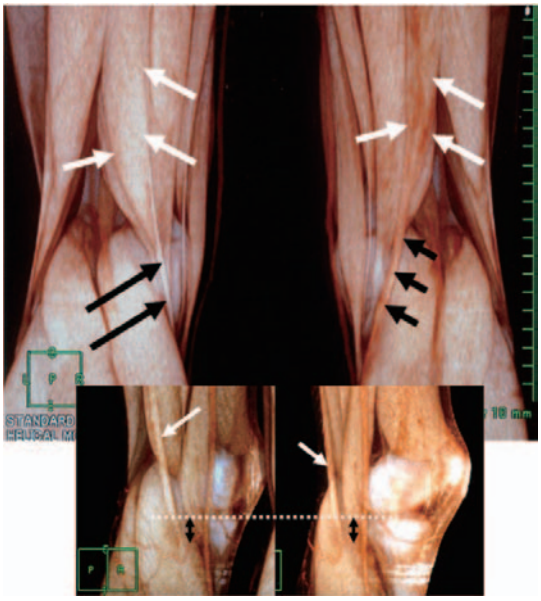
Outline

1. Background

It is desirable to maintain the morphology of the semitendinosus muscle-tendon complex after tendon harvesting for anterior cruciate ligament (ACL) reconstruction. The purpose of this study was to evaluate the influence of knee immobilization on the morphological changes in the semitendinosus muscle-tendon complex.

2. Research Summary

In total, 39 patients who underwent ACL reconstruction with autologous semitendinosus tendons were included in this study. After surgery, the knee was immobilized for 3 days in 1 group of patients (group 1; 24 patients; control group) and for a longer period (10–14 days) in the other group (group 2; 15 patients). Three-dimensional computed tomography (3D CT) examination was performed at 6 and/or 12 months after the surgery for all patients. Morphological changes in the semitendinosus muscle-tendon complex (proximal shift of the semitendinosus muscle-tendon junction, width of the regenerated semitendinosus tendons, re-insertion sites of the regenerated tendons, and rate of semitendinosus tendon regeneration) were evaluated.



3. Result

Successful regeneration of the semitendinosus tendon was confirmed in all patitents in group 2. In group 1, 3D CT showed that regeneration of the semitendinosus tendon was unsuccessful in 1 of the 24 patients. The average length of the proximal shift of the semitendinosus muscle-tendon junction was 7.3 ± 2.5 cm in group 1 and 7.2 ± 1.9cm in group 2. There were no significant differences between the 2 groups with regard to the morphological changes in the semitendinosus muscle-tendon complex.

4. For Application

The software for evaluation of the regenerate tendon's strength based on CT data is desirable.

Competitive Advantages

This study showed that the structure of regenerated tendons could be clearly identified in 38 of 39 cases (97.4%) after ACL reconstruction. However, prolonged knee immobilization (10–14 days) could not prevent morphological changes in the semitendinosus muscle-tendon complex.

Patent/Journal/Award

J Orthop Sci. 2012 Jan; 17(1): 39–45. Nakamae A, Deie M, Adachi N, Ochi M et al.
J Comput Assist Tomogr. 2005 Mar-Apr; 29(2): 241–5. Nakamae A, Deie M, Adachi N, Ochi M et al.

URL

Life Science

Development of a New Objective Diagnostic Method for Detecting Motor and Sensory Disturbance Using Higher Brain Function Analysis

Keywords Motor Disturbance, Sensory Disturbance, Diagnosis, Magnetoencephalography, Functional MRI

Kazuyoshi NAKANISHI

Department Hiroshima University Hospital

Title Assistant Professor

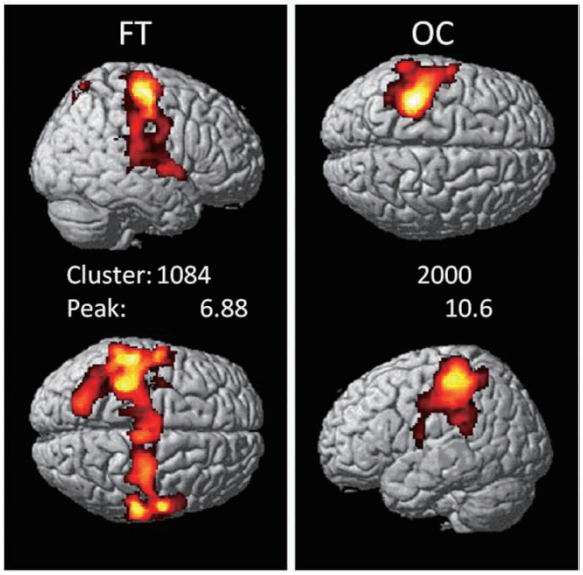
E-mail kazn@hiroshima-u.ac.jp

Field Neurophysiology

Outline

1. Background

The motor or sensory disturbance in the patients with spinal cord or peripheral nerve disorder has been evaluated subjectively, and sometimes difficult to decide its severity. Our main aim is to develop a new objective diagnostic method for detecting motor and sensory disturbance magnetoencephalography and functional MRI.



2. Research Summary

The somatosensory evoked fields were recorded using a magnetoencephalography following stimuli to the tactile pressure, pain and temperature, or joint position sense. And also brain activities were investigated using a functional MRI during motor task in the hand. Then, we will try to develop the analysis system which could evaluate for the spinal cord or peripheral nerve diseases.

3. Result

We successfully demonstrated the various activities of somatosensory cortex responses related to the hand tactile sense or paresthesia. We also showed the various activities of sensorimotor cotex responses in the patients with compressive cervical myelopathy.

4. For Application

The Interdisciplinary studies including physics, engineering, and programming should be carried out for making the methods come true.

Competitive Advantages

These concepts are quite new and innovative.

Patent/Journal/Award

Journal: 2012, HBM; 2011, Neuroreport; JBJS; 2010, Neuroci Lett; and so on.

Award: 2006, Central Association of Orthopaedic Surgery & Traumatology Award; 2007, Asahi Kasei Pharma Incentive Award.

URL

Life Science

Risk Stratification for Brugada Syndrome

Keywords Brugada Syndrome, Ventricular Fibrillation, Risk Stratification

Yukiko NAKANO

Department Hiroshima University Hospital
Title Assistant Professor
E-mail nakanoy@hiroshima-u.ac.jp
Field Cardiology, Arrhythmia

Outline

1. Background

The risk stratification for Brugada syndrome remains controversial.

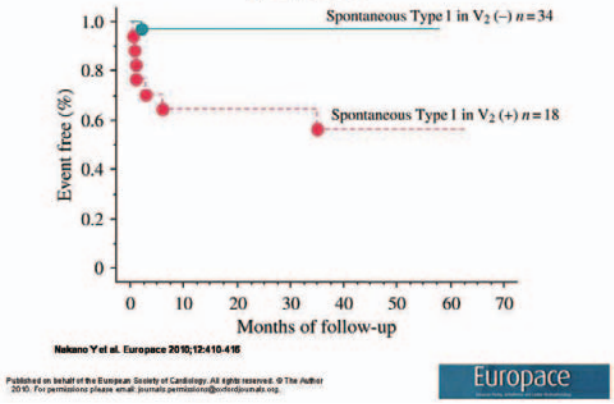
2. Research Summary

We investigated the relationships between episodes of ventricular fibrillation (VF) and various clinical, electrocardiographic, electrophysiologic, and genetic parameters both retrospectively and prospectively. Fifty-two patients with Brugada syndrome (49 men, average age 42 ± 3 years) were studied.

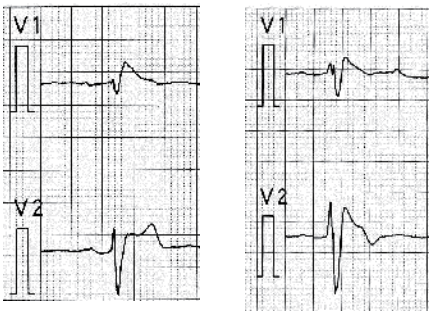
3. Result

In the Brugada patients with a VF history, the frequency of a spontaneous Type 1 electrocardiogram (ECG) pattern in lead V2 was significantly higher and the ST-J amplitude in the V1 and V2 leads was also higher than in those without a VF history. Multivariate analyses revealed that the spontaneous Type 1 ECG pattern in lead V2 (but not lead V1) was the only independent predictor of a VF history. During a mean follow-up period of 39 ± 4 months, 38.8 % of the patients with a VF history and 2.9% of those without experienced an appropriate ICD defibrillation due to VF. A multivariate analysis using a Cox's proportional hazard model showed that a VF history and spontaneous Type 1 ECG pattern in lead V2 were independent predictors of subsequent VF events.

Kaplan-Meier event-free curve of the Brugada patients with and without a Type 1 Brugada ECG pattern in lead V2



Type 1 ECG in V2 lead using 12 leads ECG



without VF　　with VF

4. For Application

Development of analysis software for risk stratification of VF risk in Brugada syndrome using 12 leads ECG.

Competitive Advantages

The12 leads ECG is a most general-purpose machine. If we can select high risk patient with asymptomatic Brugada syndrome using 12 leads ECG (morphology of V2 lead), it is very easy and will be widely used.

Patent/Journal/Award

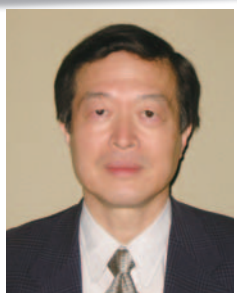
Non-SCN5A Related Brugada Syndromes: Verification of Normal Splicing and Trafficking of SCN5A Without Exonic Mutations. *Ann Hum Genet*. 71: 8–17. 2007.
Spontaneous Type 1 Electrocardiogram Pattern in the V2 Lead is an Independent Predictor of Ventricular Fibrillation in Brugada Syndrome. *Europace* 12 (3)410–6 2010.

URL

Life Science

Evaluation of Substance P Content in Biological Samples by Using a High Sensitivity Radioimmunoassay

Keywords Neuropeptide, Pain Transmitter, Inflammation

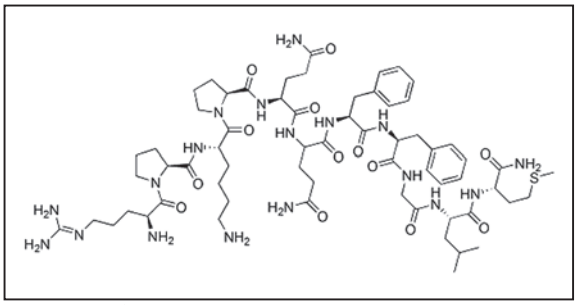


Yoshihiro NAKATA
Department Institute of Biomedical & Health Sciences
Title Professor
E-mail ynakata@hiroshima-u.ac.jp
Field Biomedical Sciences, Basic Medicine, Pharmacology

Outline

1. Background

Substance P (SP) is an 11-amino acid peptide sensory neurotransmitter, which is synthesized in the sensory neurons and released from their terminals to convey information about various noxious stimuli. It exists a small amount in a biological tissue as (pico) to n (nano) mole/g wet weight level.



Structure of Substance P

2. Research Summary

Developed a method to quantify SP in biological tissue samples using the radioimmunoassay.

3. Result

It was discovered that highly sensitive quantification of or over 10pg is possible from small amount of tissue and body fluid such as brain tissue, blood, urine and skin.

4. For Application

Quantitative analysis of SP is effective for diagnosis of inflammatory diseases and chronic pain.

Competitive Advantages

Quantification of neuropeptide may possibly become future diagnosis standards.

Patent/Journal/Award

URL http://home.hiroshima-u.ac.jp/pha

Life Science

Simple and Visible Detection Method for Drug and Poison Analysis

Keywords Detection Kit, Colorimetric, Spot Test, Drug, Agricultural Chemicals

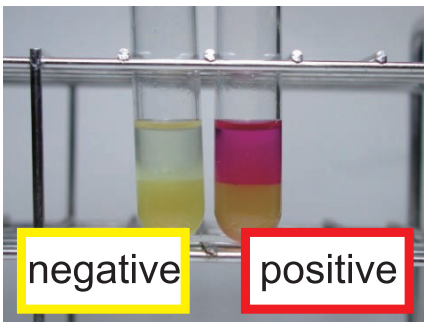
Akira NAMERA

Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail namera@hiroshima-u.ac.jp
Field Toxicology, Analytical Chemistry

Outline

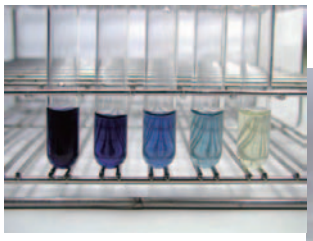
1. Background

A number of analytical methods based on chromatographic techniques are used for the determination of chemical substances. They, however, are not always useful because of complicated laboratory instruments and time-consuming sample preparations. An accurate, simple and rapid method for detection of chemical substances in biological fluids is needed which may be helpful in critical care medicine.



2. Research Summary

Colorimetric reactions, such as spot tests and Thin layer chromatography with spray to produce a color, are used for screening or preliminary identification of seized materials and residues extracted from biological materials, because it is easy to observe color changes without use of special instruments.
We researched reagents or detection methods for determination of organophosphorus pesticides or medicines, which react in aqueous solution.



3. Result

A simple method for qualitative detection of organophosphorus pesticides or medicines in human urine was developed by detecting the coloring. Thus, those proposed method is useful for qualitative analysis of these pesticides in critical care practices.

4. For Application

This colorimetric method is applied to determine the drugs or chemical substances for environmental, clinical, and toxicological laboratories.

Competitive Advantages

The detection kit will be useful for routine screening without an expensive apparatus. In addition, the time requested for sample preparation or operation will be reduced for determination of drugs and chemical substances.

Patent/Journal/Award

URL

Life Science

Yogurt Fermented by *Lactobacillus Rhamunosus* L8020, Reduce the Risks of Dental Caries, Periodontal Disease and Oral Candidosis

Keywords Probiotics, Dental Caries, Periodontal Disease, Oral Candidosis, Diabetes

Hiroki NIKAWA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail hirocky@hiroshima-u.ac.jp

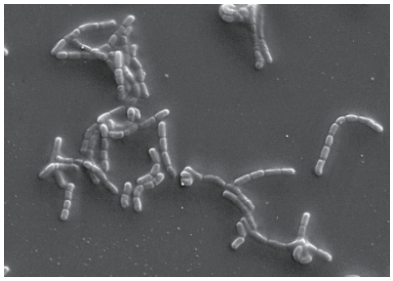
Field Prosthetic Dentistry

Outline

1. Background

Although, *genus Lactobacillus* is well-known as the co-factor of caries risks, several reports have shown that oral isolates of lactobacilli from the Caries-free patients have the potential to inhibit the growth of mutans streptococci.

The search for effective, probiotic microorganisms which reduce the risk of both caries and periodontal disease, appear to be a promising research avenue. There is however, little data available on the effect of probiotic bacteria on the oral carriage of both cariogenic and periodontal pathogens.



2. Research Summary and Results

The inhibitory effects of 42 oral isolates of lactobacilli was examined. One isolate, *L. rhamnosus* L8020, which showed the potential to inhibit either periodontal, cariogenic or fungal pathogens *invitro*, was used to examine the effects of fermented milk on the oral carriage of cariogenic and periodontal pathogens, which was examined by placebo-controlled and randamized clinical trial using 50 participants.

The eating Yogurt containing *L. rhamnosus* L8020 significantly reduced the oral carriage of mutans streptococci ($p<0.01$), and 4 kinds of periodontal pathogens examined, *i.e. Porphyromonas gingivalis* (P.g.), *Prevotella intermedia* (P.i.), *Tannerella forsythia* (T.f.), and Fusobacterium spp. (Fuso.) (P.g., P.i, T.f. and Fuso)($p<0.01$), but the phenomena were not observed with the placebo Yogurt ($p>0.05$).

3. For Application

To prepare the Freeze-Dried L8020 and incorporate them into oral moisturizing gel or Tablets.

Competitive Advantages

We have already identified the bacteriocins from L8020, which exhibits not only antimicrobial effects with wide spectra, but also inactivate the LPS from P. gingivalis, the later may contribute to reduce the risks of diabetes, or Arteriosclerosis.

Patent/Journal/Award

(1) PCT/JP2010/004626 (16.07.2010) Prophylactic, Ameliorating or Therapeutic Agent for Oral Diseases

(2) PCT/JP2012/053020 Bacteriocins derived from Lactobacillus rhamunosus.

Hiroki Nikawa, et al. Bovine milk fermented with Lactobacillus rhamnosus L8020 decreases the oral carriage of Streptococci mutans and the burden of periodontal pathogens, Journal of Investigative and Clinical Dentistry (2011), 3, 187–196, 2011

URL http://www.campusmedico.jp/l8020/index.html

Life Science

Genetic Relationships among Breeds Using Porcine Autosomal SNP Genotypes Using DNA Markers (SNPs)

Keywords DNA Marker, SNPs, Animal, Breeds, Individual Identification

Masahide NISHIBORI
Department Graduate School of Biosphere Science
Title Associate Professor
E-mail nishibo@hiroshima-u.ac.jp
Field Animal Genetics in Applied Animal Science

Outline

1. Background

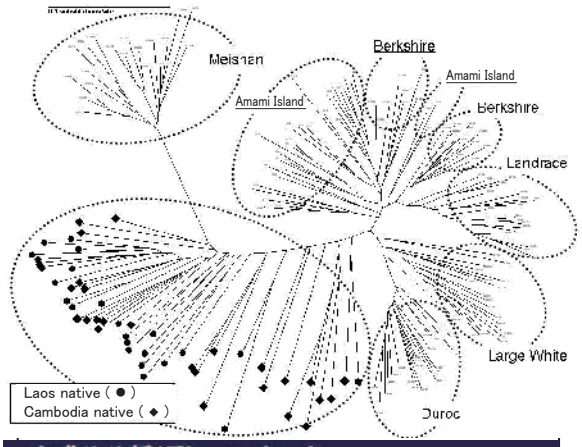
Identification of animal species, breed, and individual using molecular markers, such as DNA, requires expensive system and the operation process is complex. Thus less costly and reliable system for analysis is desired for easier detection. Present method was developed aiming to construct analysis and detection system which is also suitable for small number of population.

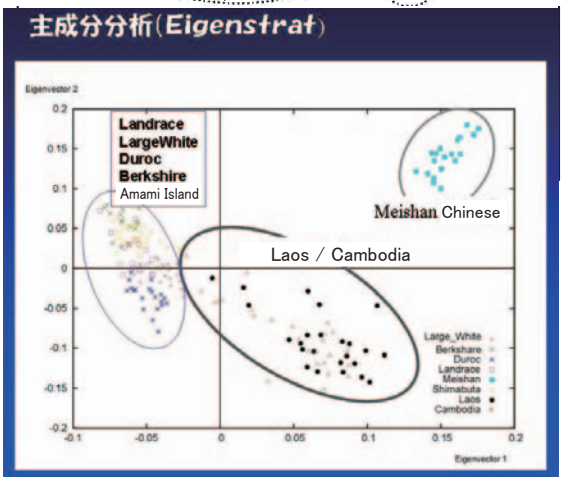
2. Research Summary

In the present study, the domestic pig, as well as the native pig of relatively low productivity which are raised in Asian countries are used as samples. SNP (Single Nucleotide Polymorphism) is used as molecular marker. By using device to recognize fluorescence for detection, low cost analysis was established. Constructed system is also capable to detect genetic diseases which affect productivity.

3. Result

9 groups of pig were divided into 11 groups. Of those, in two groups, multiple breeds existed. There is a record of past interbreeding, and it was also verified by DNA tests. The precision, general equivalence probability (*P*) of this method was calculated to be $P=1.03 \times 10^{-30}$. According to this, theoretically, it is considered at least 10^{29} pigs can be identified. According to FAOSTAT(2009), about 9.4×10^{8} pigs are raised in the world, and this means individual typing will be possible for all pigs in the world. By using this analysis method, theoretically, all pigs in the world may be identified individually. It was suggested that the SNPs detection system is useful for breed and individual identification.





4. For Application

If traceability system using individual identification number is introduced for pork in Japan and abroad, as in beef, this technology will be essential for security of products in identification of individual pig.

Competitive Advantages

Less costly and more accurate technology compared with existing DNA analysis .

Patent/Journal/Award

Oral Presentation: Nishibori, et al.(2012) “Construction of pig SNPs analysis system using DigiTag2 and application to molecular system analysis”

Japanese Society for DNA Polymorphism Research: 2011 Award for Excellent Research (Dec. 1, 2011)

URL http://dnapol.umin.jp/ (Japanese Society for DNA Polymorphism Research)

Life Science

Genetic Variant Associated with the Development of Hepatocellular Carcinoma in Japanese Chronic Hepatitis C Patients

Keywords HCV, SNP, HCC

Hidenori OCHI

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail hochi@hiroshima-u.ac.jp

Field Gastroenterology, Virology

Outline

1. Background

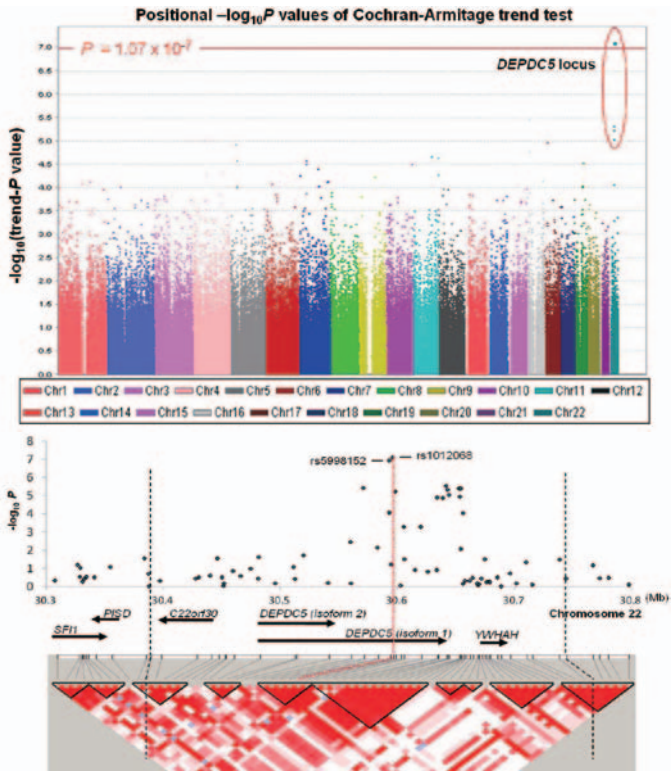
HCC is one of the most common malignancies worldwide, accounting for nearly 1 million deaths per year. The hepatitis C virus (HCV) is the major cause of HCC; approximately 70% of the HCC patients are chronically infected with HCV in Japan. The molecular mechanisms underlying development of HCC are still poorly understood.

2. Research Summary

To identify genetic risk loci for HCV related HCC, a genome-wide association study was conducted using a total of 3,312 Japanese chronic hepatitis C (CHC) patients. A total of 467,538 genetic markers (called single nucleotide polymorphisms, SNPs) were analyzed in a group of 212 CHC patients with HCC and 765 without HCC.

3. Result

One SNP rs1012068 located on DEPDC5 gene was found to be associated with HCC risk. The association was replicated in an independent cohort of 2,335 CHC patients, 710 with HCC and 1,625 without HCC. The significance of the findings was further highlighted when adjusted with confounders, revealing that the DEPDC5 SNP roughly doubles the odds of developing HCC among Japanese CHC patients.



4. For Application

This SNP could be used as a genetic marker of increased susceptibility to HCV related HCC.

Competitive Advantages

This is the first report of a genetic variant relating to HCV related HCC in japanese population using a genome-wide association study design. While advancing our understanding of the mechanisms underlying development of HCC, the discovery of the DEPDC5 variant also provides a valuable new diagnostic and therapeutic approaches against HCC.

Patent/Journal/Award

Miki D, Ochi H, Hayes CN, Abe H, Yoshima T, Aikata H, Ikeda K, Kumada H, Toyota J, Morizono T, Tsunoda T, Kubo M, Nakamura Y, Kamatani N, Chayama K. Variation in the DEPDC5 locus is associated with progression to hepatocellular carcinoma in chronic hepatitis C virus carriers. Nat Genet 2011

URL http://www.nature.com/ng/journal/v43/n8/full/ng.876.html

Life Science

Articular Cartilage Repair with Magnetically Labeled Mesenchymal Stem Cells and External Magnetic Device

Keywords Magnetically Labeled Mesenchymal Stem Cells, External Magnetic Device, Cartilage Repair

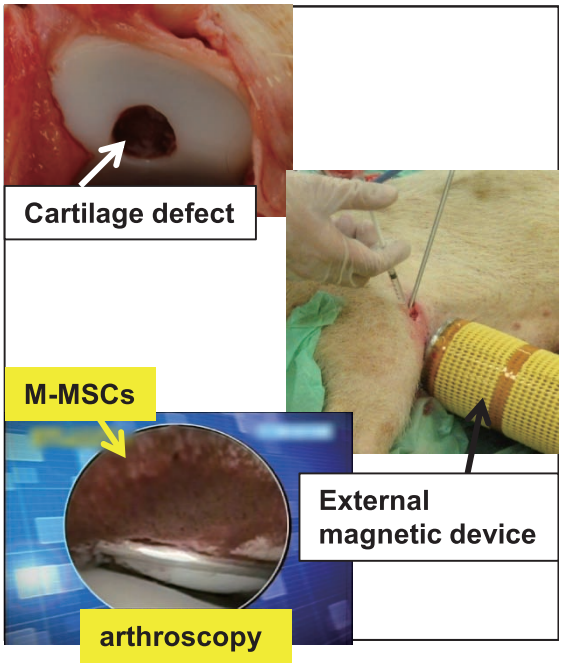
Mitsuo OCHI

Department Institute of Biomedical & Health Sciences
Title Professor
E-mail ochim@hiroshima-u.ac.jp
Field Orthopaedic Surgery

Outline

1. Background

Recently, numerous studies have been reported to evaluate the cartilage repairs using MSCs. However, in these studies, MSCs can't be accumulated to a cartilage defect without scaffold, and a large number of MSCs for cartilage regeneration are needed to treat a large cartilage defect. Intra-articular injection of too many MSCs was reported to generate loose bodies of scar tissue in the joint in the rat model. Therefore, to provide effective chondral defect treatment, it is essential to inject a small number of MSCs into the defect site. We developed a novel cell delivery system for regenerated medicine using MSCs with superparamagnetic iron oxide (magnetically labeled MSCs: m-MSCs) and an external magnetic device to accumulate a relatively small number of MSCs to a desired area.



2. Research Summary

Full-thickness cartilage defect (6mm diameter) in the center of the patella. Four weeks after creation of cartilage defect, for magnetic force group, m-MSCs (5×106 cells) were injected and accumulated to the cartilage defect using an external magnetic force (1.5 Tesla) for 10 minutes. For gravity group, the patella was faced upward, filled with MSCs (5×106 cells) and held for 10 minutes. For the control group, PBS was injected. Porcine were sacrificed at 3 and 6 months, and macroscopical, histological and ultrasonic evaluation was done.

3. Result

This study showed that we could obtain better hyaline-like cartilage regeneration by accumulating relatively small number of m-MSCs to the cartilage defect using external magnetic force.

4. For Application

We should assess the tumorgenecity of m-MSCs for clinical application. We are developing the smaller external magnetic device.

Competitive Advantages

This method enables us to accumulate MSCs to cartilage defect effectively without scaffold. Therefore, we expect early and better cartilage regeneration compared to MSC injection method.

Patent/Journal/Award

URL

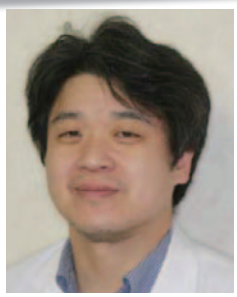
Life Science

CX3CL1 Expression Induced by *Candida Albicans* in Oral Fibroblasts

Keywords *Candida albicans*, CX3CL1

Kouji OHTA

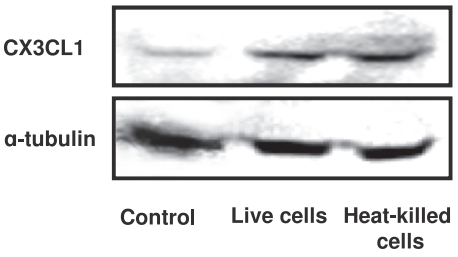
Department Hiroshima University Hospital
Title Assistant Professor
E-mail otkouji@hiroshima-u.ac.jp
Field Oral Surgery



Outline

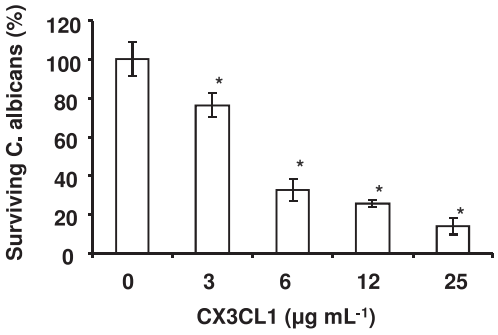
1. Background

Oral candidiasis is a superficial mucosal infection primarily caused by *Candida albicans*, the principal species responsible for intraoral infections. *C. albicans* penetrates at microscopic wound sites where the epithelial integrity is weak. When the *C. albicans* reaches the basal epithelial layer, invasion of the adjacent connective tissue can follow. Therefore, oral fibroblasts as well as keratinocytes apparently participate in host defense against *C. albicans.*



2. Research Summary

In the present study, we hypothesized various chemokines in oral fibroblasts participate in host defense against *C. albicans*. We first determined which chemokines in oral fibroblasts are influenced by *C. albicans*. Thereafter, we tested the antifungal activity of the chemokine domain of CX3CL1, which strongly affected by *C. albicans* in oral fibroblasts.



3. Result

We examined the effects of *C. albicans* live cells on the mRNA expressions of 12 different chemokines in oral fibroblasts.

C. albicans live cells caused a 10-fold increase of only CX3CL1 mRNA levels among tested chemokines. CX3CL1 protein was detected in oral fibroblasts stimulated with *C. albicans* live or heat-killed cells. Interestingly the chemokine domain of CX3CL1 showed significant antifungal activity against *C. albicans*

4. For Application

We demonstrated that oral fibroblasts produce CX3CL1 in response to *C. albicans*, and that CX3CL1 has antifungal activities against C. albicans. CX3CL1 may be useful as marker for oral candidiasis or anti-fungal peptide.

Competitive Advantages

Few reports showed oral fibroblast has antifungal peptide. Oral fibroblasts appear to play an important role in oral immune response to *C. albicans* infection.

Patent/Journal/Award

Ohta K et al. FEMS medical microbiology and immunology, 2010 Nov; 60(2): 179–85.

URL

Life Science

Statistical Analysis of Multidimensional Data of Complex Systems

Keywords Questionnaire Survey, Data Analysis, Mathematical Modelling of Carcinogenesis, Statistical Analysis, Risk Analysis

Megu OHTAKI

Department Research Institute for Radiation Biology and Medicine

Title Professor

E-mail ohtaki@hiroshima-u.ac.jp Field Biometrics, Environmetrics, Applied Statistics, Epidemiology

Outline

1. Background

To explore the mathematical structure of data concerning complex systems with uncertainty in bio-medical or environmental field.

2. Research Summary

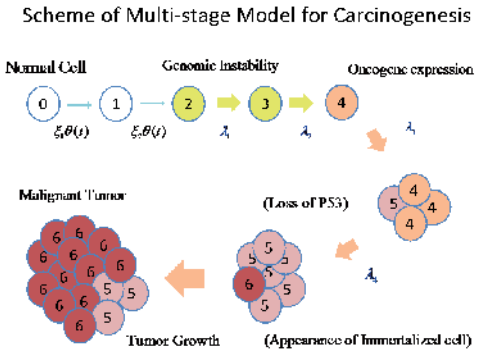
Spatial-time distribution of cancer risk among atomic bomb survivors was explored. On the basis of survey data, the spatial distribution of black rain falling just after the bombing was estimated. A theory and computer software for estimating source-apportionment of air pollution was developed. A simple method for analyzing microarray data to search for state of gene expression was developed.

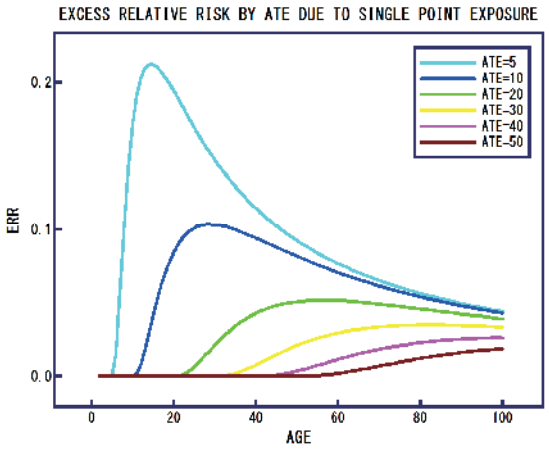
3. Result

Mathematical structures for exploring various multi-dimensional spatial-time data in bio-medical or environmental science fields were explored quantitatively.

4. For Application

There exist possible contribution to searching the optimal system and factors for the improvement of human health, QOL and for prevention of cancer.





Competitive Advantages

Using mathematical models based on a highly useful knowledge about real science, we analyze actual data to create high value-added new findings.

Patent/Journal/Award

U.S. Patent No.: US 6,932,363 B2, patent acquisition date: August 16, 2005, Title: Storage medium for the projection method of searching for direction enabled, the system, programs, and housing programs:

URL

Life Science

Biodiversity and Ecology of Marine Symbionts and Parasites; Fisheries of Edible Zooplankters

Keywords Marine Plankton, Jellyfish, Crustaceans, Symbiosis, Parasitism

Susumu OHTSUKA

Department Graduate School of Biosphere Science

Title Professor

E-mail ohtsuka@hiroshima-u.ac.jp

Field Fisheries Science, Biodiversity, Phylogeny

Outline

1. Background

Since symbiotic interactions among marine planktonic, nektonic and benthic organisms and the fisheries of edible jellyfish and pelagic crustaceans in Southeastern Asia are little known, we have intensively been investigating these fields.

2. Research Summary

Recently we have carried out the following studies: (1) taxonomy, life cycle, development and ecology of copepods parasitic on cultured fish in Japan; (2) symbiotic interactions between jellyfish and fish/invertebrates (see right figure); (3) fisheries of edible jellyfish and pelagic crustaceans in Southeastern Asia

Butterfish associated with Japanese sea nettle

3. Result

The life cycle, development and ecology of sea lice on cultured tiger puffer and red sea bream have been revealed by our studies. Symbiotic interactions between jellyfish and fish/ invertebrates have been clarified using modern techniques with stable isotopes. The current fisheries of edible jellyfish and pelagic crustaceans in Thailand and Indonesia have been scientifically investigated.

4. For Application

Advises and scientific supports for fisheries and environmental assessment companies; enlightenment education on marine biology for educational facilities

Competitive Advantages

Pioneering studies by our scientific activities: current conditions of fisheries of edible jellyfish and pelagic crustaceans in Thailand and Indonesia; taxonomy and ecology of pathogenic copepods in fish farms; symbiotic interactions in marine zooplankton communities

Patent/Journal/Award

Prize from the Japanese Society of Systematic Zoology; Excellent Paper Award (The Oceanographical Society of Japan), Excellent Paper Award (The Zoological Society of Japan)

URL http://home.hiroshima-u.ac.jp/fishlab/

Life Science

Unite for Stroke

Keywords Stroke

Toshiho OHTSUKI

Department Hiroshima University Hospital
Title Associate Professor / Lecturer
E-mail aaatoshi@hiroshima-u.ac.jp
Field Neurology

Outline

1. Background

As a clinician in duty and charge of treatment of stroke in the acute stage, I tackle this serious and frequent disease which occurs suddenly in one's later stage of life, leaving intractable after effects such as hemiplegia, aphasia, cognitive impairment, etc. that distress the patient and his/her family.

2. Research Summary

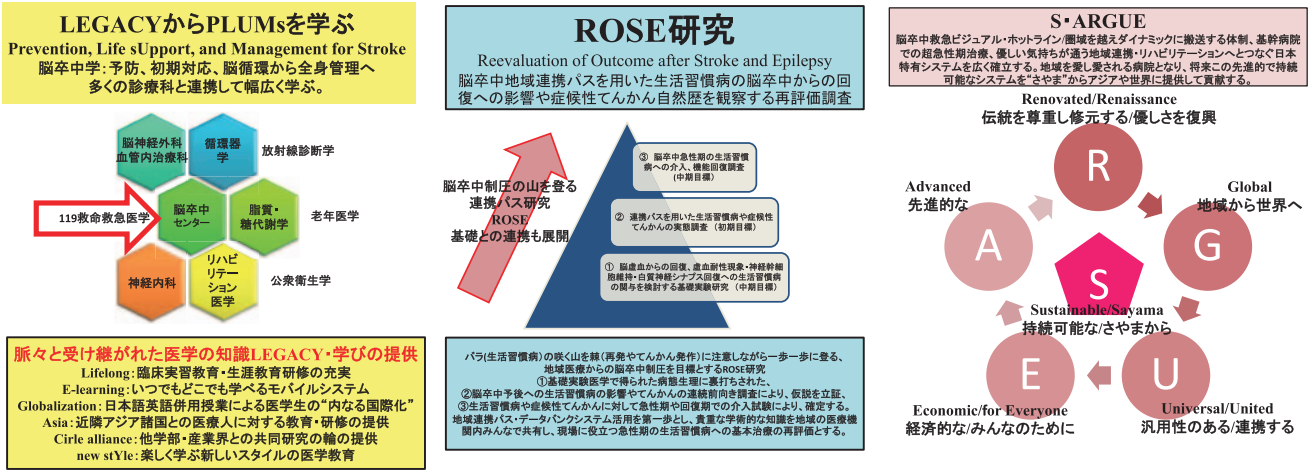
Obesity/underweight and recovery from stroke
Hyperuricemia and neurological worsening after acute stroke
Fluctuation of blood glucose and clinical outcome in diabetic stroke patients
α-galactosidase enzymatic activity of juvenile stroke
Relationship between Ehlers–Danlos syndrome, Marfan syndrome, and cerebral artery dissection
Treatment of hereditary vascular dementia Development of metabolic rehabilitation
Research on locomotive syndrome after stroke
Long term prognosis of stroke complicated by infectious endocarditis
Application of robotics for neuro-rehabilitation after stroke

3. Result

Research is on-going.

4. For Application

Accumulating basic data which may be adopted in guidelines of stroke treatment.



Competitive Advantages

Based on steady epidemiologic research, sincerely examine and treat each patient, to bring results from accompanying and caring medical services. Value the principle of maximizing patient's own Resilience.

Patent/Journal/Award

"Prevention of intracranial hemorrhage." In Japanese Guidelines for the Management of Stroke. On *J. Stroke Cerebrovasc. Dis.* 20 (2011) s75–77.
Japanese Stroke Society-Japan Heart Association Kusano Award for "Influence of oxidative stress on induced tolerance to ischemia in gerbil hippocampal neurons" in *Brain Res*. 599 (1992) 246–252.

URL

Life Science

Caries Incidence Associated with *Streptococcus Mutans* and *S. Sobrinus* in Children

Keywords Prevention of Dental Caries

Mitsugi OKADA

Department Hiroshima University Hospital

Title Professor

E-mail mitsugi@hiroshima-u.ac.jp

Field Social Dentistry

Outline

1. Background

We detected *Streptococcus mutans* and *S. sobrinus* in children using polymerase chain reaction method, to compare their presence with dental caries experience.

2. Research Summary

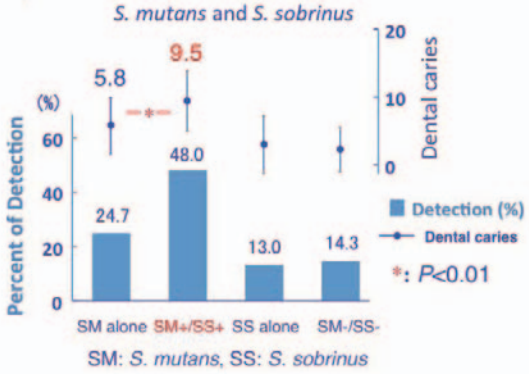
Children harboring both *S. mutans* and *S. sobrinus* have a significant higher dental caries experience in both permanent and primary teeth as compared to those with *S. mutans* alone.

3. Result

Overall, dental caries scores of subjects positive for *S. mutans* and *S. sobrinus* were significantly higher than the scores of those positive for *S. mutans* alone (P<0.05).

Dental caries scores of subjects positive for both *S. mutans* and *S. sobrinus* at baseline and after 1 year were significantly higher than those positive for *S. mutans* alone at the same stages (P<0.01, P<0.001, respectively). The caries incremental increase was also significantly greater in those with both bacteria detected (P<0.05).

Caries prevalence in children with *S. mutans* alone or both *S. mutans* and *S. sobrinus*



Caries prevalence in children with S. mutans alone or in combination with S. sobrinus at baseline and after 1 year

MS		Dental caries		Percent of increase		Increase in caries
S. mutans	*S. sobrinus*	n	%	n	%	
+	-	11	90.9	3	27.3	0.5
+	+	20	95.0	15	75.0	2.0
-	+	9	77.8	2	22.2	
-	-	7	28.6	1	14.3	

4. For Application

Mutans streptococci are strongly associated with the development of dental caries in humans. It is of great importance to detect the presence of mutans streptococci in children for dental caries prediction and subsequent treatment.

Competitive Advantages

Conventional polymerase chain reaction assays have been found suitable for specific detection and identification of human cariogenic bacteria, including *S. mutans* and *S. sobrinus*.

Patent/Journal/Award

1) PCR detection of *Streptococcus mutans* and *S. sobrinus* in dental plaque samples from Japanese pre-school children. Okada M, et al. J Med Microbiol. 2002 May; 51(5): 443–7.

2) Longitudinal study of dental caries incidence associated with *Streptococcus mutans* and *Streptococcus sobrinus* in pre-school children. Okada M, et al. J Med Microbiol. 2005 Jul; 54(7): 661–5.

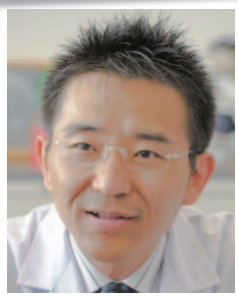
3) Caries prevalence associated with *Streptococcus mutans* and *Streptococcus sobrinus* in Japanese schoolchildren. Okada M, et al. Int J Paediatr Dent. 2012 Jan 8. doi: 10.1111/j.1365–263X.2011.01203.x. [Epub ahead of print]

URL

Life Science

Upregulation of Notch2 and Six1 is Associated with Progression of Early-stage Lung Adenocarcinoma and a More Aggressive Phenotype at Advanced Stages

Keywords Cancer, Lung, Adenocarcinoma



Morihito OKADA

Department Research Institute for Radiation Biology and Medicine

Title Professor

E-mail morihito@hiroshima-u.ac.jp

Field Thoracic Surgery

Outline

1. Background

Lung adenocarcinoma often manifests as tumors with mainly lepidic growth. The size of invasive foci determines a diagnosis of in situ, minimally invasive adenocarcinoma, or invasive types and suggests that some adenocarcinomas undergo malignant progression in that order. This study investigates how transcriptional aberrations in adenocarcinoma cells at the early stage define the clinical phenotypes of adenocarcinoma tumors at the advanced stage.

2. Research Summary

We comprehensively searched for differentially expressed genes between preinvasive and invasive cancer cells in one minimally invasive adenocarcinoma using laser capture microdissection and DNA microarrays. We screened expression of candidate genes in 11 minimally invasive adenocarcinomas by reverse transcriptase PCR and examined their involvement in preinvasive-to-invasive progression by transfection studies. We then immunohistochemically investigated the presence of candidate molecules in 64 samples of advanced adenocarcinoma and statistically analyzed the findings, together with clinicopathologic variables.

3. Result

The transcription factors Notch2 and Six1 were upregulated in invasive cancer cells in all 11 minimally invasive adenocarcinomas. Exogenous Notch2 transactivated Six1 followed by Smad3, Smad4, and vimentin, and enlarged the nuclei of NCI-H441 lung epithelial cells. Immunochemical staining for the transcription factors was double positive in the invasive, but not in the lepidic growth component of a third of advanced Ads, and the disease-free survival rates were lower in such tumors.

4. For Application

Paired upregulation of Notch2 and Six1 is a transcriptional aberration that contributes to preinvasive-to-invasive adenocarcinoma progression by inducing epithelial-mesenchymal transition and nuclear atypia. This aberration persisted in a considerable subset of advanced adenocarcinoma and conferred a more malignant phenotype on the subset.

Competitive Advantages

Patent/Journal/Award

Clin Cancer Res 2012; 18: 945–955.

URL

Life Science

Identification of Responsible Genes for Patients with Chronic Mucocutaneous Candidiasis

Keywords Chronic Mucocutaneous Candidiasis, Primary Immunodificiency, STAT1

Satoshi OKADA

Department Hiroshima University Hospital

Title Assistant Professor

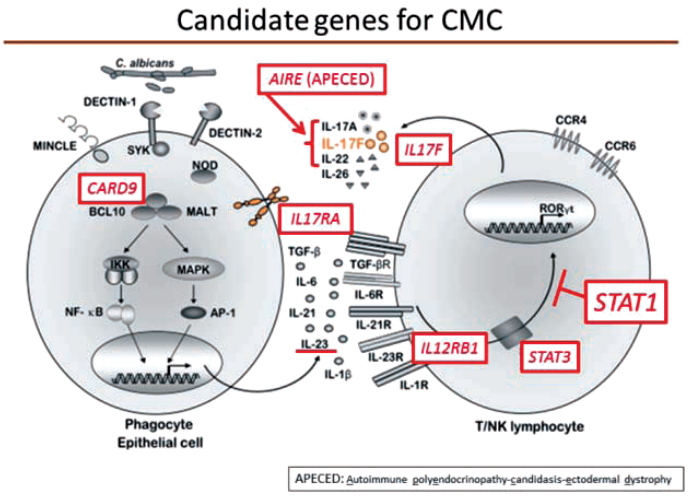
E-mail s-okada@pg8.so-net.ne.jp

Field Biology, Medicine, Pediatrics

Outline

1. Background

Chronic mucocutaneous candidiasis (CMCD) is characterized by persistent or recurrent disease of the nails, skin, oral or genital mucosae caused by *Candida albicans*. The patients also suffer from autoimmune disorders. Although several candidate genes are recently discovered, no genetic etiology has yet been identified for most patients with CMCD.



2. Research Summary

We investigated familial and sporadic cases with CMCD. We used following three approaches to identify responsible genes; i) candidate gene approach, ii) honozygous mapping, iii) whole-exome sequence. From the results of whole-exome sequence, we identified heterozygous mutation in *STAT1* in patients with CMCD. Functional analysis was done using patients' EBV-B cells and transient gene expression experiments. We also investigated patients' PBMCs and identified that Th17 cells decreased in the patient.

3. Result

We identified gain-of-function mutations in STAT1 as a genetic cause of CMCD. STAT1 mutation was identified in approximately 40% of patients with CMCD. We also identified that patients with STAT1 mutation show decreased number of Th17 cell in PBMCs.

4. For Application

We can use these results for diagnosis and genetic counseling of patients with CMCD.

Competitive Advantages

We identified gain-of-function mutations in *STAT1* as genetic causes for patients with CMCD. Our research may provide a new approach for treatments of patients with CMCD based on the better understanding of this disorder.

Patent/Journal/Award

Liu L, Okada S, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 208: 1635–1648, 2011 (equal authorship).

URL

Life Science

Research Infrastructure for Conducting a Safe and Secure Cell Therapy Using Mesenchymal Stem Cells Derived from Human Bone Marrow

Keywords Dentistry, Regenerative Medicine

Kosei OKAMOTO

Department Hiroshima University Hospital
Title Assistant Professor

E-mail kohsei@hiroshima-u.ac.jp
Field Dentistry

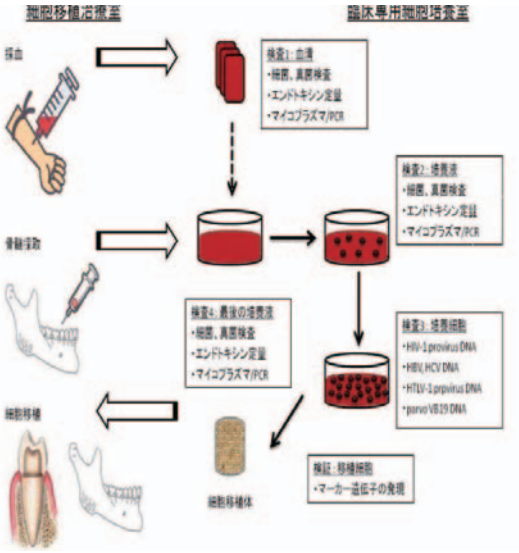
Outline

1. Background

For clinical application of regenerative medicine using stem cells, objectively assess and classify risks and ensure the safety, and expand the strategy to the cell therapy using stem cells which are a source of cells leading to regenerative medicine .

2. Research Summary

On applications of regenerative medicine using stem cells, conditions for suitable culture to maintain cultured cells, evaluation of proliferative potential and differentiation potential of stem cells, elucidation of the molecular mechanism of inflammation and immunity adjustment, transformation, safety and risk management analysis were considered.



3. Result

It has been suggested that the medium with TGF-β1 added to serum-free medium for human ES cells promotes the proliferation of human mesenchymal stem cells which maintain pluripotency of undifferentiated.

4. For Application

The ability to maintain pluripotency of undifferentiated in serum-free medium may lead to possible clinical applications.

Competitive Advantages

In practice of regenerative medicine, the significance of ensuring quality and safety of the cells is extremely large, and with confirmation of safety and efficiency, this will play a central role in regenerative medicine research in the future.

Patent/Journal/Award

URL

Life Science

Screening of Useful Materials from Unculturable Bacterial Metagenomes

Keywords Marine Bacteria, Metagenome, Bio-active Compound, Useful Material Production

Yoshiko OKAMURA

Department Graduate School of Advanced Sciences of Matter

Title Associate Professor

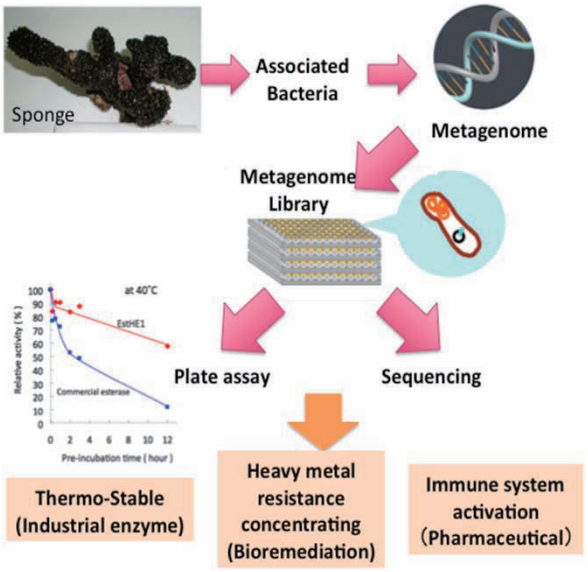
E-mail okamuray@hiroshima-u.ac.jp

Field Genome Science, Process engineering

Outline

1. Background

So far, genome engineering of microorganisms was limited among established strains. However, it was revealed that the ocean has far more unculturable microorganisms than those found on land and that 99.9% of marine microorganisms discovered are difficult to culture. Several bioactive compounds have known to be produced by uncultured bacteria that are thriving in marine sponges. Therefore, we focused on metagenomic research whereby the DNA of these marine microorganisms are extracted, analyzed and studied.



2. Research Summary

The metagenomic libraries and their database have been constructed with DNA isolated from marine sponge-associated bacteria to find novel genes and unique mechanisms.

3. Result

The esterase, a member of rare family, showing high thermo-stability and unique characteristics and the genes involving in concentrating and resistance for heavy metal, respectively, were isolated. Now, we found the factors affecting the immune response. The structural study and characterization of these are ongoing.

4. For Application

Almost of isolated genes from metagenomes are novel or low homology with known genes. The metagenomes are good gene resources. These novel factors or the strategies may contribute to find pharmaceuticals for solving unmet medical needs problems.

Competitive Advantages

Screening of interests from library brings not only bio-active products but coding genes, therefore, this strategy has an advantage in establishing the production systems. Furthermore, to obtain novel genes or having low homology with known genes has an advantage over patented genes.

Patent/Journal/Award

Okamura et al. Mar. Biotechnol. (2010)

URL

Life Science

Assessment of the Safety Behavior in the Workplace

Keywords Safety Behavior, Safety Culture, Safety Climate, Accident Prevention

Yasumasa OTSUKA

Department Graduate School of Education

Title Associate Professor

E-mail yasumasa-otsuka@hiroshima-u.ac.jp

Field Clinical Psychology, Social Psychology, Social System Engineering/Safety System

Outline

1. Background

Evaluating the levels of workers' safety behavior is important to prevent occupational accidents.

2. Research Summary

Questionnaire was developed based on the interviews conduced for railway employees and safety experts. Questionnaires consisting of these items were distributed for railway employees.

3. Result

Occupational safety behavior questionnaire consisting of five subscales (communication about safety, daily safety activity, keep own safety, keep own equipment safely, and seek information about safety) with forty items was developed.

Department	No. of Respoundents	Date of Questionnare				
	Average	Assessment (Mark Applicable Scale)				
		A	B	C	D	E
communication about safety		45.0~52.0	42.1~44.9	36.3~42.0	33.4~36.2	13.0~33.3
daily safety activity		37.9~40.0	35.6~37.8	31.2~35.5	28.9~31.1	10.0~28.8
keep own safety		27.0~32.0	25.1~26.9	21.2~25.0	19.3~21.1	8.0~19.2
keep own equipment safely		19.9~24.0	18.1~19.8	14.7~18.0	12.9~14.6	6.0~12.8
seek information about safety		10.8~12.0	9.9~10.7	8.1~9.8	7.2~8.0	3.0~7.1
Risk of Accidents/Injuries		・(Sample) Work at a high place → fall (Risk: 4) ・ ・ ・				

4. For Application

This questionnaire could be used for assessing the levels of workers' safety behavior, especially for dangerous work at the manufacturing company, etc. This may also be used for assessing the risks at the workplace.

Competitive Advantages

To our knowledge, no other questionnaires which can evaluate the multiple aspects of workers' safety behavior in this kind of short form were exist.

Patent/Journal/Award

Otsuka Y & Suzuki A (2006). Development of the safety behavior scale and its differences by job types: Questionnaire survey for employees working in railway systems or their affiliated companies. *Anzen Kogaku*, 45, 25–33.

Japan National Institute of Occupational Safety and Health (2011). Stress management manual for preventing the accidents in the workplace.

URL

Life Science

Probabilistic Considerations on Eclosion and Copulation of Cicadas

Keywords Cicadas, Probability, Eclosion, Copulation

Yasumasa SAISHO

Department Graduate School of Engineering
Title Associate Professor

E-mail saisho@hiroshima-u.ac.jp
Field Mathematics, Probability Theory, Mathematical Biology

Outline

1. Background

Since cicadas are difficult to keep, many ecological problems are left open.

2. Research Summary

In this study we construct a stochastic model and handle the following two problems. The first problem is the peak period of copulations of cicadas. The second problem is to consider the relation between the sexual difference of eclosion periods and copulation ratio of female cicadas.

3. Result

The delay of eclosion of females promotes an increased copulation rate or the total copulation times of the population.

4. For Application

No application is assumed now.

Competitive Advantages

Some clues to appear ecological problems of cicadas are given by this research.

Patent/Journal/Award

Y. Saisho, Mathematical observations on the relation between eclosion periods and the copulation rate of cicadas, Mathematical Biosciences and Engineering, 7–2 (2010), 443–453.

Akitsu Prize (The Entomological Society of Japan)

URL

Life Science

Development of Method to Screen Novel Therapeutical Drugs for Neurodegenerative Disease Using Imaging Technique

Keywords Pharmacology, Neuroscience, Neurodegenerative Disease

Norio SAKAI

Department Institute of Biomedical & Health Sciences

Title Professor

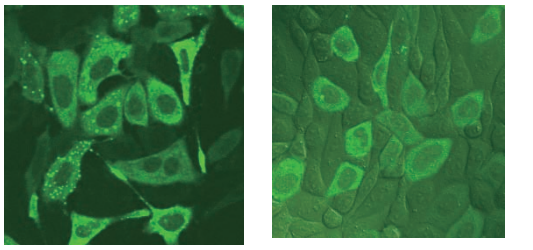
E-mail nsakai@hiroshima-u.ac.jp

Field Pharmacology, Neurochemistry, Neuropharmacology

Outline

1. Background

Spinocerebellar ataxia type 14 (SCA14) was caused by mutation of gamma PKC, neuron specific PKC subtype. We have investigated the molecular mechanism how mutant gamma PKC leads to neurodegeneration. Here, we propose the method to screen novel therapeutical drugs for neurodegenerative disease according to the character of SCA14 mutant gamma PKC.



No treatment　　Trehalose **0.1mM**

SCA14 mutant gamma PKC-GFP was expressd in SH-SY 5Y cells. Treatment of trehalose reduced the aggregation of mutant gamma PKC.

2. Research Summary

We expressed the mutant gamma PKC-GFP in neuronal cell lines, and revealed that mutant gamma PKC-GFP tented to aggregate and cause cell death. By quantifying the extend of aggregation, we attempted to find the candidate drugs for neurodegenerative disease.

3. Result

We found that trehalose and congo red reduced the toxicity of mutant gamma PKC by inhibiting the formation of its aggregation. This result shows the utility of this method for screening novel therapeutical drugs for neurodegenerative disease.

4. For Application

Development of automatic screening method, Provision of chemincals

Competitive Advantages

Mutant gamma PKC is a molecule with high mobility, which can easily form aggregates in the cell.

Patent/Journal/Award

Japanese Patent Application No. JP2007–65448 Screening of novel drugs for neurodegenerative disease

J. Pharmacol. Sci. 114 (2010) 206–216

J Biol. Chem. 285 (2010) 33252–33264

URL

Life Science

Evaluation of Dural Arteriovenous Fistulas of Cavernous Sinus before and after Endovascular Treatment Using Time-resolved MR Angiography

Keywords Cavernous Sinus, Digital Subtraction Angiography, Dural Arteriovenous Fistulas, Endovascular Treatment, Time-resolved Magnetic Resonance Angiography

Shigeyuki SAKAMOTO

Department Hiroshima University Hospital

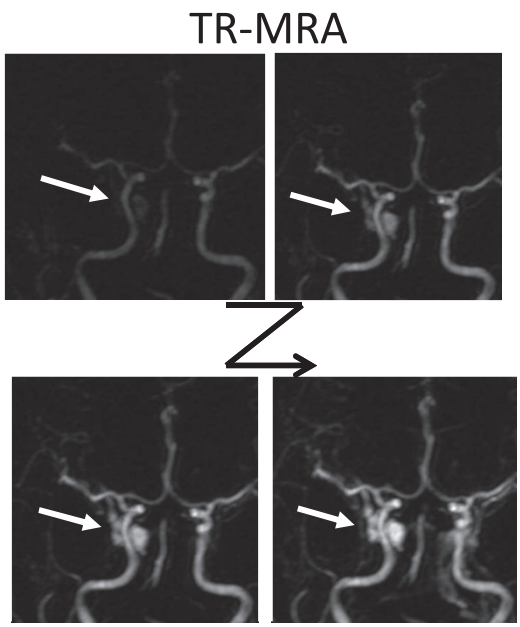
Title Assistant Professor

E-mail professorsakamoto@hiroshima-u.ac.jp Field Neurosurgery

Outline

1. Background

Digital subtraction angiography (DSA) is the preferred method for confirming dural arteriovenous fistulas (DAVFs), but it has the disadvantage of being invasive. In contrast, time-resolved magnetic resonance angiography (TR-MRA) is a useful, noninvasive imaging technique. The aim of this study was to compare the evaluation of DAVFs of the cavernous sinus (CS) using TR-MRA and DSA.



2. Research Summary

TR-MRA and DSA were obtained in 6 patients with CS-DAVFs treated with endovascular surgery. TR-MRA and DSA before and after treatment were reviewed by one neuroradiologist without previous knowledge of the existence of CS-DAVFs for the detection and characterization (feeding artery and venous drainage) of CS-DAVFs.

3. Result

TR-MRA could detect and diagnose CS-DAVF. However the details regarding anatomical feeders and draining veins remain poorly visualized by TR-MRA.

4. For Application

TR-MRA can be a useful screening tool to detect CS-DAVF and possibly also to confirm persistent obliteration following definitive treatment.

Competitive Advantages

The role of TR-MRA for estimating CS-DAVF before and after endovascular treatment became clear.

Patent/Journal/Award

Neurosurgical Review Award of Hiroshima clinical surgery medical society

URL

Life Science

Application of Thermally Stable Cytochrome c

Keywords Cytochrome c, Protein, Thermal Stability

Yoshihiro SAMBONGI

Department Graduate School of Biosphere Science

Title Professor

E-mail sambongi@hiroshima-u.ac.jp

Field Agricultural Chemistry, Frontier Agriculture

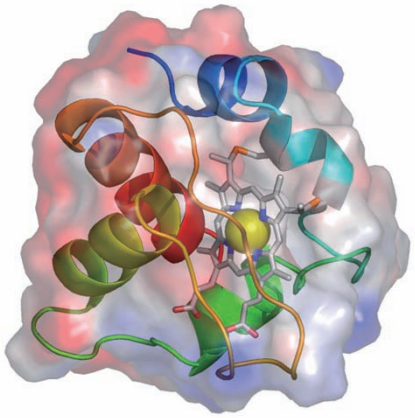
Outline

1. Background

Thermally stable proteins may be useful for application.

2. Research Summary

Form bacteria living in high and low temperature, and in high pressure, cytochrome c proteins are isolated. Their thermal stability and electron transfer activity are investigated.



3. Result

Cytochromes c from high temperature or high pressure environments are thermally stable. A specific cytochrome c is stable up to the temperature of 130 °C.

4. For Application

The thermally stable cytochrome c can be used as molecular chip.

Competitive Advantages

This research is characteristic in the way that we can prepare thermally stable cytochrome c through our own bio-production system.

Patent/Journal/Award

Yamanaka, M., Masanari, M., **Sambongi, Y**. Conferment of folding ability to a naturally unfolded apocytochrome c through introduction of hydrophobic amino acid residues. *Biochemistry*, 50, 2313–2320 (2011).

URL http://www.hiroshima-u.ac.jp/gsbs/kyouin/senmon/index.html

Life Science

Prediction of Human Drug Metabolism and Pharmacokinetics Using Chimeric Mice with Humanized Liver

Keywords Chimeric Mice with Humanized Liver

Seigo SANOH

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

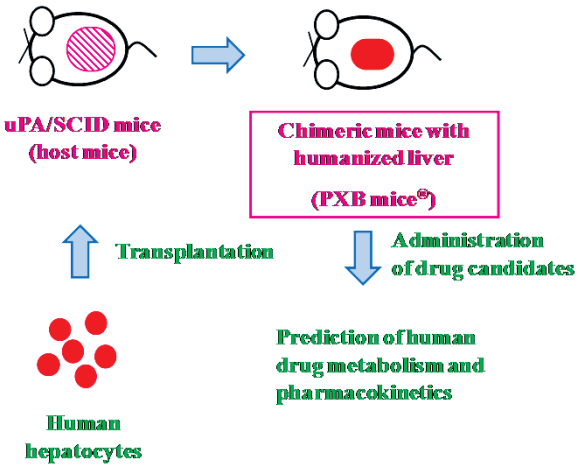
E-mail sanoh@hiroshima-u.ac.jp

Field Pharmaceutical Sciences

Outline

1. Background

It is important to predict human drug metabolism and pharmacokinetics in the pre-clinical stage of pharmaceutical development to reduce costs and drop-out rate by enabling the early selection of drug candidates with unsuitable properties. Accurate approaches for human predictions have been required in pharmaceutical industries.



Prediction of human drug metabolism and pharmacokinetics using chimeric mice with humanized liver (PXB mice®)

2. Research Summary

We used chimeric mice with humanized liver (PXB mice®, PhoenixBio, Co., Ltd, Higashi-Hiroshima, Japan, by collaborative work) which have been generated from uPA/SCID translated with human hepatocytes. The expression levels and metabolic activities of drug metabolic enzymes in liver of PXB mice® were similar to those in humans. Thus, PXB mice® could be a good in vivo model for predicting drug metabolism and pharmacokinetics in humans.

In this work, we selected 13 model compounds that are metabolized by several drug metabolic enzymes in liver and compared the profiles in humans to evaluate the utility of PXB mice® for human prediction .

3. Result

Drug metabolism and pharmacokinetic profiles in PXB mice® after administration of 13 model compounds were similar to those of human.

4. For Application

Our results suggest that PXB mice® may be helpful for prediction of human metabolism and pharmacokinetics of drug candidates which are metabolized by several metabolic enzymes in liver during pre-clinical stage of pharmaceutical development.

Competitive Advantages

Various approaches to predict human drug metabolism and pharmacokinetics with in vitro metabolic system, such as human hepatocytes, have been reported but with partially limited success. We could evaluate not only in vitro but also in vivo profiles from chimeric mouse data.

Patent/Journal/Award

Sanoh *et al., Drug Metabolism and Disposition*, 40(1) 76–82.

Sanoh *et al., Drug Metabolism and Disposition*, 40(2) 322–328.

URL

Life Science

Assessment of Trypsinogen-2 levels as an Early Diagnostic for Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis

Keywords Post-ERCP Pancreatitis, Trypsinogen-2, Early Diagnosis

Tamito SASAKI

Department Hiroshima University Hospital

Title Associate Professor / Lecturer

E-mail tamito@hiroshima-u.ac.jp

Field Internal Medicine, Gastroenterology

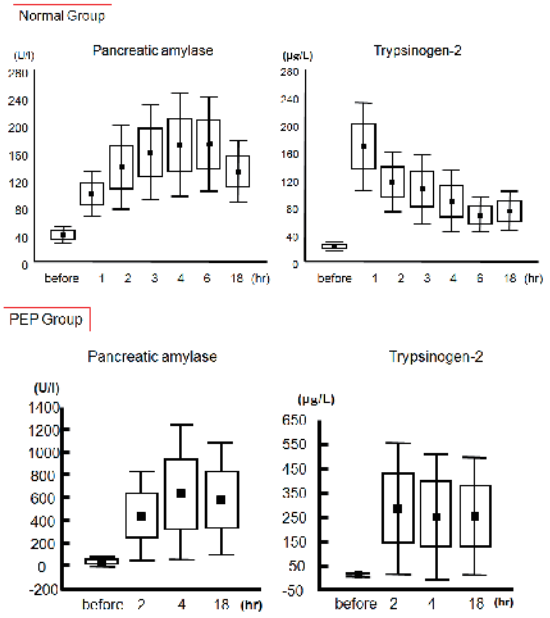
Outline

1. Background

Endoscopic retrograde cholangiopancreatography (ERCP) has become an invaluable procedure for examination and treatment of pancreaticobiliary diseases. Nonetheless, post-ERCP acute pancreatitis is a complication that does occur and can be fatal.

2. Research Summary

In this prospective study, blood serum both before and at 1, 2, 3, 4, 6, and 18 hours after ERCP were collected, and total amylase, pancreatic amylase, and trypsinogen-2 levels were measured from serum samples, and values from patients with pancreatitis after ERCP (PEP) were compared to those from 'normal' control patients after ERCP



3. Result

In the normal group, total- and pancreatic-amylase levels peaked four hour after ERCP, and trypsinogen-2 levels peaked at one hour after ERCP. In contrast, PEP cases demonstrated prolonged periods of high total-amylase, pancreatic-amylase, and trypsinogen-2 levels.

4. For Application

Trypsinogen-2 is a more sensitive marker than amylase and that it can be useful in early diagnosis PEP.

Competitive Advantages

The alteration of trypsinogen-2 is correlated with PEP and those measurement after ERCP is able to reduce patient's risk with PEP.

Patent/Journal/Award

Pancreas. 2011 Nov; 40 (8): 1206–10.

URL

Life Science

Functional Model of Temporomandibular Joint

Keywords Model, Temporomandibular Joint, Jaw Movement

Takahiro SATODA

Department Institute of Biomedical & Health Sciences

Title Professor

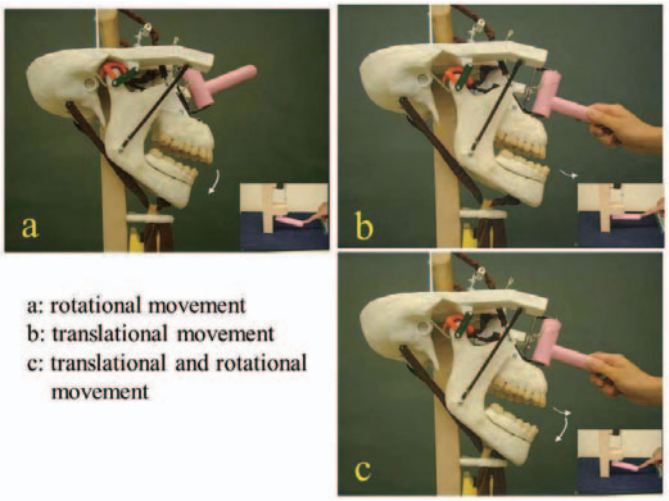
E-mail satoda@hiroshima-u.ac.jp

Field Dentistry, Education, Anatomy

Outline

1. Background

Temporomandibular joint (TMJ) is the joint between the temporal bone and the condyle of the mandible. The articular disc divides the TMJ into the superior and inferior compartments. Superior compartment provides for translational movement. Inferior compartment provides for rotational movement.



a: rotational movement
b: translational movement
c: translational and rotational movement

2. Research Summary

Here we made a model in order to explain this complicated jaw movement. The skull is made of wood and paper clay. Mandible is made of paper clay with metallic plate in it. Lateral ligament is made of metallic plate. Muscles are made with the wires. Inferior head of the lateral pterygoid is connected to the lever. Using this model, we can easily explain the jaw movement.

3. Result

Using this model, we can easily explain the mechanism of the Jaw movement.

4. For Application

A commercialized model will target dental colleges, dental hygienists' schools and dental technicians' schools as potential buyers.

Competitive Advantages

This kind of model is not commercially available. We consider this model to be superior to computer graphics.

Patent/Journal/Award

URL

Life Science

Functional Model of Swallowing

Keywords Swallowing, Anatomy Education

Takahiro SATODA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail satoda@hiroshima-u.ac.jp

Field Dentistry

Outline

1. Background

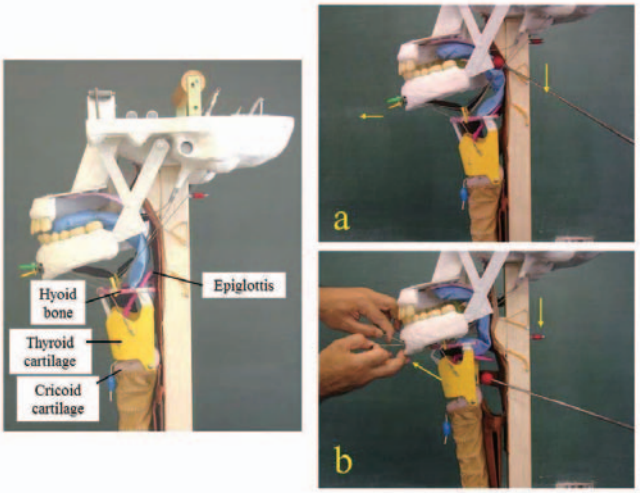
Swallowing is moving a bolus of food from the oral cavity to the esophagus. The bolus of food is propelled to the back of the mouth by the tongue and swallowing reflex occurs. After the oral cavity and nasopharynx closure, the glottal closure occur, then hyoid bone and larynx are lifted by the contraction of the suprahyoid and thyrohyoid muscles. Pharyngeal constrictor muscles compress the bolus and a slight vacuum occurs in the orifice of the esophagus.

2. Research Summary

Here we made a model in order to explain this complicated swallowing mechanism. Mandible is made of paper clay by using a metallic plate in it. The tongue and soft palate and epiglottis are made by the EVA(Ethylene Vinyl Acetate) sheet. A movable wooden chip represents the contraction of the pharyngeal constrictor muscles. The upper part of the esophageal constrictor is made with spring plates.

3. Result

Using this model, we can easily explain the mechanism of the swallowing.



a:bolus is in oral part of pharynx
b:suprahyoid and throhyoid muscles lift the pharynx

4. For Application

A commercialized model will target, dental colleges, dental hygienists' schools and dental technicians' schools as potential buyers.

Competitive Advantages

This kind of model is not commercially available. We consider this model to be superior to the computer graphics.

Patent/Journal/Award

Acta Anatomica Nipponica 83: 51–59 ,2008

URL

Life Science

Statistical Data Analysis

Keywords Statistical Analysis, Data Mining, Text Mining

Kenichi SATOH

Department Research Institute for Radiation Biology and Medicine

Title Associate Professor

E-mail ksatoh@hiroshima-u.ac.jp Field Statistical Science

Outline

1. Background

Recently recording and storing data are getting easy, but using them efficiently is still hard.

2. Research Summary

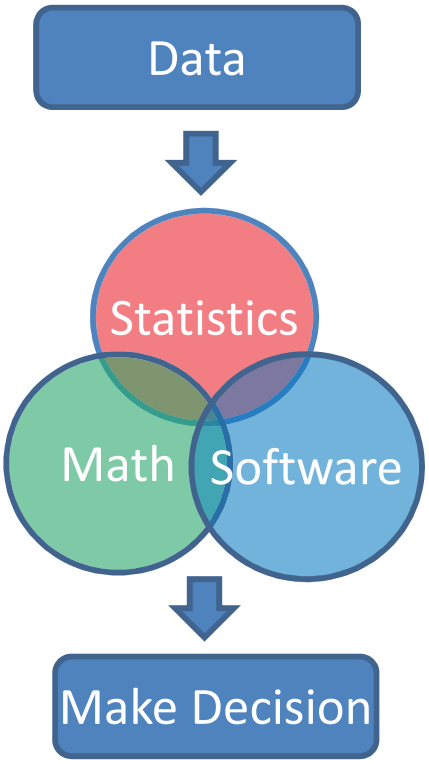
Statistical consulting, developing statistical methods and software

3. Result

Original papers including data analysis (60), attending international conference (6), invited talk (4).

4. For Application

Statistical consulting and lectures on statistical software can be supplied.



Competitive Advantages

Statistical analysis can put a “probability” on a data processing.

Patent/Journal/Award

The Best Paper of the Year (Japanese Journal of Applied Statistics, 2010)

URL http://home.hiroshima-u.ac.jp/ksatoh/cv.htm

Life Science

Statins Induce Apoptosis and Inhibit Proliferation in Cholangiocarcinoma Cells

Keywords Statin, Apoptosis, Cholangiocarcinoma

Masahiro SERIKAWA
Department Hiroshima University Hospital
Title Assistant Professor
E-mail serikawa@hiroshima-u.ac.jp
Field Internal Medicine, Gastroenterology

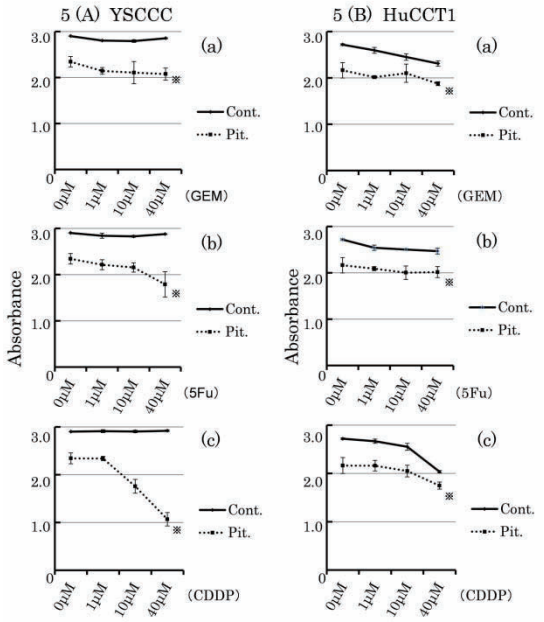
Outline

1. Background

Given the poor prognosis for cholangiocarcinoma, new and effective treatments are urgently needed. HMG-CoA reductase inhibitors (statins) reportedly exert anticancer effects in a variety of diseases, but there have been no reports of these effects in cholangiocarcinoma.

2. Research Summary

Proliferation suppression by pitavastatin and atorvastatin was investigated in the human cholangiocarcinoma cell lines HuCCT1 and YSCCC while changes in the cell cycle and intracellular signals were examined by FACS and Western blotting, respectively. Additive proliferation suppression by statins and pre-existing anticancer drugs was also investigated.



3. Result

HuCCT1 and YSCCC cell proliferation was dramatically suppressed by incubation with statins for 72 h or longer. Cell cycle analysis revealed a reduction in the G2M fraction and an increase in the sub-G1 fraction in statin-treated cells, while Western blotting showed increased levels of cleaved caspase-3 and a reduction in p-ERK. Furthermore, statins in combination with gemcitabine, cisplatin and 5-FU showed additive proliferation suppression.

Competitive Advantages

In this study, treatment of human cholangiocarcinoma cells with statins induced apoptosis via suppression of the classical MAPK pathway. Together, these results suggest that statins may be a new cholangiocarcinoma treatment option that could potentially enhance the anticancer effect of pre-existing anticancer drugs.

Patent/Journal/Award

Int J Oncol. 2011 Sep; 39(3): 561–8.

URL

Life Science

A Novel Pig Artificial Insemination Technique Using Frozen-thawed Sperm

Keywords Artificial Insemination, Cryopreservation, Pig Production

Masayuki SHIMADA

Department Graduate School of Biosphere Science

Title Associate Professor

E-mail mashimad@hiroshima-u.ac.jp

Field Animal Science

Outline

1. Background

Cryopreservation of boar sperm offers an effective means for long-term storage of important genetic material. This technique solves the problem of transporting animals or fresh semen over long distances. However, cryopreserved boar sperm are not routinely available to swine producers because conception litter size have remained low when the frozen-thawed sperm have been used for artificial insemination. Because the technique consists of 5 parts, we developed novel sperm handling technique, cooling method from 37 °C to 5 °C, freezing method under liquid nitrogen, thawing technique and artificial insemination.

2. Research Summary

We observed bacteria infection, mostly gram negative bacteria, in more than 70 % of boar. The secreted endotoxin, LPS directly acts on boar sperm to decrease the sperm motility. From this result, we developed the novel sperm handling method using polymixin B. During cooling process, solution of the sperm is resuspended with hyper-osmotic extender containing egg yolk to decrease free water from inside of sperm, and cooled slowly from 15 °C to 5°C for 90 min. During thawing process, the increase of intercellular Ca^{2+} ($[Ca^{2+}]_i$) in sperm induces the cryo-capacitation and loss of acromal cap, which reduces the sperm motility after culture. We add Ca^{2+} chelator to thawing solution to prevent sperm damage of frozen-thawed sperm.

3. Result

Using frozen-thawed boar sperm, more than 80% of conception rate and more than 10 piglets are predicted by artificial insemination. This technology is a major breakthrough bringing the same result for key breeds including Landrace, Large White, Duroc and Berkshire. In addition, we developed an extender to transfer the semen at room temperature. Using the extender, the good quality frozen semen was produced after the semen was left for 2 days. This enables freezing semen of the sires being bred at a remote location.

4. For Application

- Production/sales of freeze preservation solution
- Production of frozen sperm by pig farmers
- Contract production service by our venture

Competitive Advantages

Artificial insemination using frozen-thawed boar sperm technology is not prevelent in Japan due to low conception and small number of piglets. The overseas technology is not advanced and has cost issues. Establishment of this technology has significant competitive advantages.

Patent/Journal/Award

Patent: PCT/JP2010/060320 filed on 17.06.2010, SPERM DILUENT SOLUTION AND METHOD FOR ARTIFICIAL INSEMINATION USING SAME, by Hiroshima University & Oita Prefecture

Paper: Okazaki T, Mihara T, Fujita Y, Yoshida S, Teshima H, Shimada M.
Poand cryopreservationlymyxin B neutralizes bacteria-released endotoxin and improves the quality of boar sperm during liquid storage. *Theriogenology* 2010 74(9): 1691–1700.

URL

Life Science

Intracellular Behavior and Elimination of Extrachromosomal Elements

Keywords Gene Amplification, Extrachromosomal Element, Micronuclei, Protein Production

Noriaki SHIMIZU

Department Graduate School of Biosphere Science

Title Professor

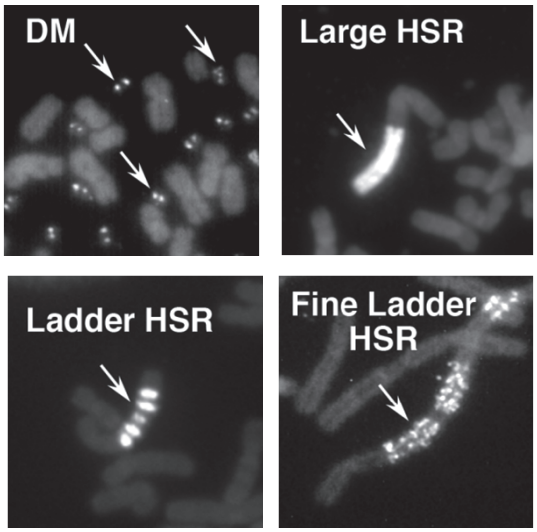
E-mail shimizu@hiroshima-u.ac.jp

Field Applied Molecular and Cellular Biology

Outline

1. Background

Gene amplificaiotn plays a pivotal role in mammalian carcinogenesis through the over production of e.g. oncogene product. The amplified genes localize either at the extrachromosomal Double Minutes (DMs) or the chromosomal homogeneously staining region (HSR).



2. Research Summary

To uncover the mechanism that govern the intracellular behavior and the elimination to the extracellular space of the extrachromosomal DMs.

3. Result

I have developed a novel scientific field on how the extrachromosomal elements behave in the nucleus during the cells cycle progression, how they are segregated to doughter cells, how they move to the cytoplasm and how they are eliminated from the cells.

4. For Application

Development of a non-viral vector that is stably maintained in mammalian cells. (Basic research stage)

Competitive Advantages

Patent/Journal/Award

URL http://home.hiroshima-u.ac.jp/shimizu/index.html

Life Science

Mechanism of Gene Amplification and its Application to the Protein Production

Keywords Gene Amplification, Extrachromosomal Element, Micronuclei, Protein Production

Noriaki SHIMIZU

Department Graduate School of Biosphere Science

Title Professor

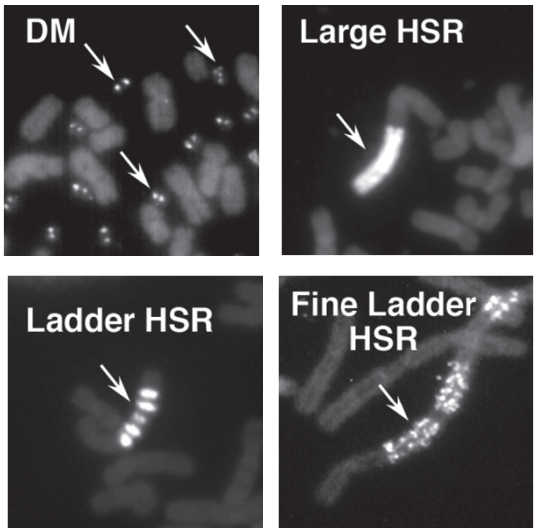
E-mail shimizu@hiroshima-u.ac.jp

Field Applied Molecular and Cellular Biology

Outline

1. Background

Gene amplification plays a pivotal role in mammalian carcinogenesis through the over production of e.g. oncogene product. The amplified genes localize either at the extrachromosomal Double Minutes (DMs) or the chromosomal homogeneously staining region (HSR).



2. Research Summary

To uncover the mechanism of gene amplification that is mediated by the extrachromosomal elements, and to apply our achievement to the industrial protein production.

3. Result

I found that the plasmid with a mammalian replication initiation region (IR) and a nuclear matrix attachment region (MAR) is efficiently amplified in mammalian cells and generate DMs and/or HSR. I uncovered the mechanism underlying it, and applied the system to the industrial protein expression.

4. For Application

Establishment of cells that stably produce high amount of recombinant protein pharmaceuticals (industrial stage).

Competitive Advantages

Compared to the conventional technologies, we may more rapidly and easily develop cell lines that more stably produce higher amount of recombinant antibody pharmaceuticals.

Patent/Journal/Award

There are 5 already listed patents, 7 patents under application, including 5 PCT applications.

URL http://home.hiroshima-u.ac.jp/shimizu/index.html

Life Science

Research and Development to Minimize the Impact of Electromagnetic Radiation on the Human Body for Hybrid Vehicles and Electric Vehicles Parts

Keywords Next-generation Vehicle Development, Hybrid Vehicle, Plug-In Hybrid Vehicle, Electric Vehicle, Electromagnetic Wave, Power Electronics

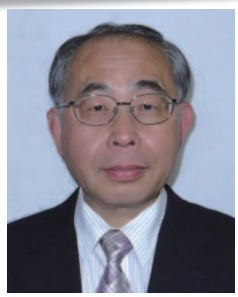
Kenji SHODAI

Department Center for Collaborative Research & Community Cooperation

Title Professor (Special Appointment)

E-mail shodai@hiroshima-u.ac.jp

Field Electric/Electronic



Outline

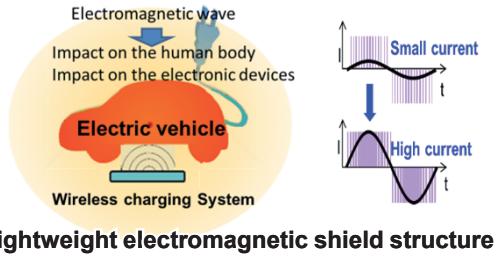
1. Background

To create a competitive hybrid vehicle and electric vehicle parts industry in the Hiroshima area, establish a high-efficiency power electronics technology that considers the protection of the human body from electromagnetic waves.

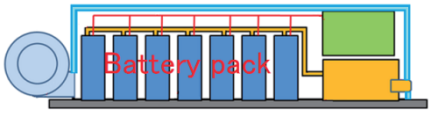
2. Research Summary

In inverters and converters used in hybrid vehicles and electric vehicles, because of switching large currents at high frequencies, large electromagnetic waves occur.

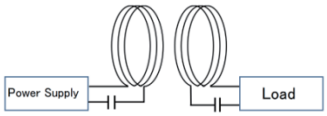
In order to ensure that these electromagnetic waves do not affect the human body and other electronic equipment, conduct research and development of power electronics and lightweight electromagnetic shield structure with less unwanted radiation.



Lightweight electromagnetic shield structure



Wireless charging system (no effect on the human body)



3. Result

Since start in December 2011, we have completed the research and development to narrow the target.

- Technology research foundation for protection of the human body from electromagnetic wave
- Light electromagnetic shield of power electronics equipment
- Magnetic resonance wireless charging system

We have completed the composition of the research project that consists of local companies, research institutions and government agencies.

4. For Application

Can be utilized to power electronics components of hybrid vehicles, plug-in hybrid vehicles and electric vehicles.

It is necessary to improve the technology of local companies car electronics, due to low accumulation of Automotive Electronics Technology.

Competitive Advantages

The metal shield is being used for electromagnetic shielding of power electronics, but in the next-generation car, weight reduction is a major issue.

Aim to develop a lightweight power electronics and electronic equipments which are safe and secure for people.

Patent/Journal/Award

URL

Life Science

Development of Simulator for Extracorporeal Circulation

Keywords Spinal Cord Protection, Atrial Fibrillation, Simulator, Extracorporeal Circulation

Taijiro SUEDA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail sueda@hiroshima-u.ac.jp

Field Cardiovascular Surgery

Outline

1. Background

Development of simulator for extracorporeal circulation

2. Research Summary

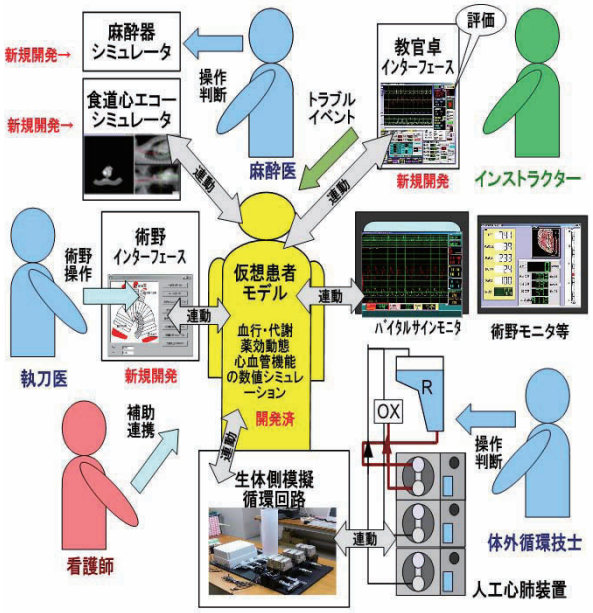
Simulator for extracorporeal circulation was developed. This simulator is already commercially available.

3. Result

New simulator for extracorporeal circulation was developed and was sold as commercial article.

4. For Application

We took 3 patents (no.3774769, no.4284418, no4867001 and 1 patent unexamined publication 2009–217042.



Competitive Advantages

This simulator was recognized as the best simulator for training of extracorporeal circulation in the world by the American Society for Extracorporeal Circulation. This simulator is the only Japanese simulator for extracorporeal circulation and used in the hands-on training during the congress of the Japanese Society for Artificial Organ and the Japanese Society for Thoracic Surgery.

Patent/Journal/Award

We took 3 patents already and 1 unexamined publication regarding simulator of extracorporeal circulation. I received the best technology prize of the Japanese Society for Artificial Organs in 2010. Also I received the first prize for Hiroshima University Intellectual Property Award in 2010 with the 18 patents granted.

URL

Life Science

Spinal Cord Protection during Thoracic Aortic Aneurysm

Keywords Spinal Cord Protection, Atrial Fibrillation, Simulator, Extracorporeal Circulation

Taijiro SUEDA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail sueda@hiroshima-u.ac.jp

Field Cardiovascular Surgery

Outline

1. Background

Spinal cord protection during thoracic aortic aneurysm surgery

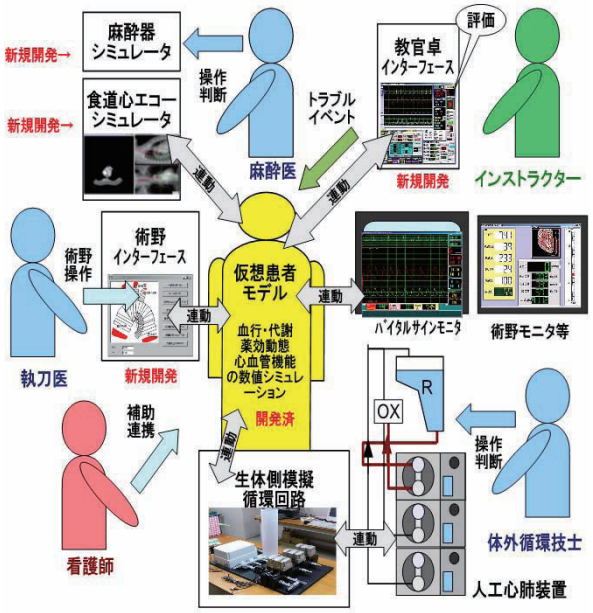
2. Research Summary

Spinal cord protection during thoracic aortic aneurysm, using motor-evoked potential and spilnal cord plesia. Also developed spinal local cooling device.

3. Result

Spinal cord protection during thoracic aortic aneurysm, using motor-evoked potential and spinoplesia. We used these methods for clinical cases and reported many experimental and clinical papers.

4. For Application



Competitive Advantages

Patent/Journal/Award

2 Japanese patents application pending (one of the 2 also applied for the U.S.).

I received the first prize for Hiroshima University Intellectual Property Award in 2010 with the 18 patents granted.

URL

Life Science

Surgery for Atrial Fibrillation

Keywords Spinal Cord Protection, Atrial Fibrillation, Simulator, Extracorporeal Circulation

Taijiro SUEDA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail sueda@hiroshima-u.ac.jp

Field Cardiovascular Surgery

Outline

1. Background

Surgery for atrial fibrillation

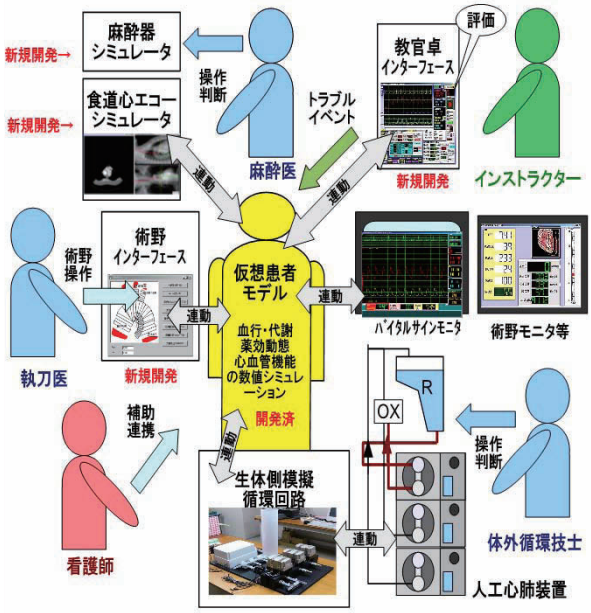
2. Research Summary

Surgery for atrial fibrillation was devised by clarifying mechanism of atrial fibrillation

3. Result

Surgery for atrial fibrillation was devised and revealed good clinical results. This surgery resolved the mechanism of atrial fibrillation

4. For Application



Competitive Advantages

Patent/Journal/Award

I received the first prize for Hiroshima University Intellectual Property Award in 2010 with the 18 patents granted.

URL

Life Science

Neuronal Bases of Pleasure and Displeasure for Taste

Keywords Taste, Neuron

Makoto SUGITA

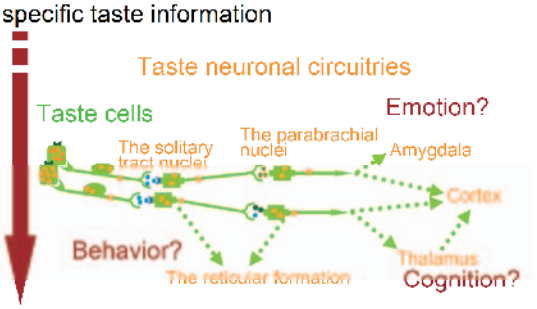
Department Institute of Biomedical & Health Sciences
Title Professor
E-mail sugisan@hiroshima-u.ac.jp
Field Functional Basic Dentistry, Physiology in General

Outline

1. Background

The taste system is primarily devoted to a quality check of food. Humans detect and distinguish among sweet, bitter, salty, sour and umami stimuli. The five basic tastes are mediated by separate classes of taste receptor cells in the tongue. However, it remains elusive how tastes are represented in the brain, and how taste information evokes specific behavioral and emotional responses while activating specific populations of neurons.

Visualizing the neuronal circuitries transmitting specific taste information



Clarifying the cellular functions of the visualized neurons

2. Research Summary

To clarify the molecular, cellular and system mechanisms underlying taste cognition and taste-evoked behavioral and emotional responses, it is necessary to understand and compare the contrastive neuronal circuitries that process the information of aversive and attractive taste modalities in the brain. By selectively expressing a fluorescent transneuronal tracer in specific taste receptor cells, and by visualizing the locations of neurons in the brain, which are labeled by the tracer originating from them, we mapped connections formed by small subsets of neurons that process specific taste information.

3. Result

Spatial distribution of the tracer-labeled neurons revealed the neuronal bases that underlie taste cognition, and provided insight into how taste information is translated in the brain into appropriate behavioral and emotional responses.

4. For Application

To develop the therapeutics to treat taste disorder, eating disorder, hyperphagia, anorexia and obesity
To create the strategies to alleviate displeasure on taking bitter medicine.

Competitive Advantages

The ability to visualize neurons labeled by the fluorescent transneuronal tracer that originated from a given cell type provides a unique opportunity to understand the physiological functions of neurons in the specific neuronal circuitries by analyzing the live neurons.

Patent/Journal/Award

Sugita, M., Shiba, Y. (2005) Genetic tracing shows segregation of taste neuronal circuitries for bitter and sweet. Science, 309, 781–785.

URL

Life Science

See-through Frogs Created by Breeding

Keywords See-through Frogs, Artificial Breeding, Color Mutants, Experimental Model Animals

Masayuki SUMIDA

Department Graduate School of Science
Title Professor
E-mail msumida@hiroshima-u.ac.jp
Field Basic Biology

Outline

1. Background

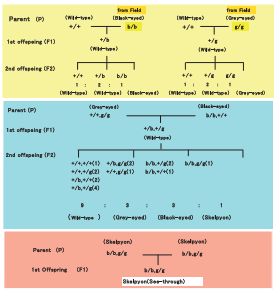
The skins of frogs are generally covered with dermal chromatophore units consisting of xansophores, iridophores and melanophores, so the internal organs cannot be seen through the skin. Although some small fish are see-through, see-through tetrapods have never been reported. The primary purpose of this study is to create the experimental model animal of which organs can be observed over its entire life without dissection.

See-through tadpole

2. Research Summary

Two kinds of recessive color mutants (black-eyed and gray-eyed) are known to lack the normal iridophores and melanophores in the Japanese brown frog *Rana* japonica, respectively, and cause the frogs to be pale or albino. These two color mutants were bred and maintained in the Institute for Amphibian Biology of Hiroshima University. We crossed these two kinds of color mutant frogs through artificial insemination, and F2 offspring led to frogs whose skins are see-through throughout life.

See-throug frog, two color mutants and wild-type



Creation of see-through frogs

3. Result

See-through frogs require no dissection and allow repeated observation of the viscera of a single frog over its entire life. They are useful in investigating the growth, maturation, and aging of the viscera as well as the development and progression of cancer. Researchers can also observe how toxins affect bones, the liver and other organs at low cost. You can watch organs of the same frog over its entire life, as you don't have to dissect it. Dramatic changes of organs can be also seen when tadpoles metamorphose into frogs.

4. For Application

See-through frogs can be used as experimental model animal in the various fields such as medicine, veterinary, biology, and education. Production and marketing business for see-through frogs (skelpyons) may be applied for ornamental purposes. Genetic engineering could also produce see-through and even illuminating frogs.

Competitive Advantages

See-through frogs can also reproduce, with their offspring inheriting their parents' traits, but their grandchildren die shortly after birth. As they have two sets of recessive genes, something wrong must kick in and kill them. In see-through frogs, xansophores are still normal. If we can produce the frogs lucking xansophores, we can get the completely see-through frogs.

Patent/Journal/Award

Japanese Patent Application Number: JP2006–203987 "Creation and Use of See-through Frogs"

URL http://home.hiroshima-u.ac.jp/~amphibia/sumida/

Life Science

Clinical Application of an Artificial Nerve for Peripheral Nerve Injury

Keywords Peripheral Nerve, Artificial Nerve

Osami SUZUKI

Department Hiroshima University Hospital
Title Assistant Professor

E-mail osami@hiroshima-u.ac.jp
Field Biology, Medical, Orthopaedic Surgery

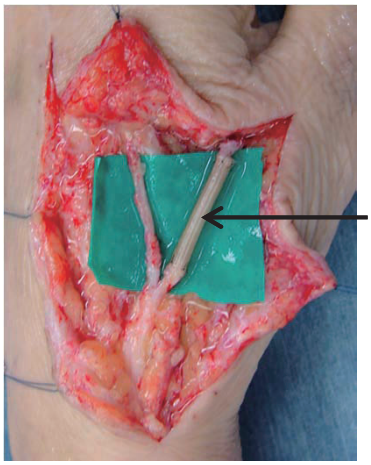
Outline

1. Background

Although peripheral nerve defect has been treated with autologous nerve graft, donor morbidity is inevitable. Artificial nerve has a potential to be a treatment option without such morbidity.

2. Research Summary

Artificial nerve (RNTC06, Toyobo co.,ltd, Japan) was grafted in clinical practice and functional outcome was compared with that of autologous nerve graft. This research was performed as a multicenter study at 19 hospitals in Japan.



Artificial nerve grafted for the nerve defect

3. Result

Functional outcome of artificial nerve was same level as that of autologous graft.

4. For Application

It is close to clinical use, because the outcome was excellent without severe side effects.

Competitive Advantages

Artificial nerve has a potential to be a treatment option without donor morbidity.

Patent/Journal/Award

URL

Life Science

Treatment of Arthritis Using MicroRNA Th17 Cell Differentiation

Keywords Arthritis, Rheumatoid Arthritis, Th17 cell, MicroRNA

Osami SUZUKI

Department Hiroshima University Hospital

Title Assistant Professor

E-mail osami@hiroshima-u.ac.jp

Field Biology, Medical, Orthopaedic Surgery

Outline

1. Background

Th17 cell differentiation is deeply-committed to disease state of arthritis including rheumatoid arthritis. Controlling Th17 cell differentiation has a potential to treat arthritis.

2. Research Summary

Some microRNAs will control Th17 cell differentiations (Table). They were injected to animal model of arthritis and the change of disease situation was observed.

	miRNA ID	Expression ratio	p value
6 miRNAs up-regulated	let7a	2.119413042	0.01219878
	hsa-miR-26a	1.812510994	0.02939706
	hsa-miR-146a	1.43106906	0.04019598
	hsa-miR-146b	1.802918862	0.03959604
	hsa-miR-150	1.605962505	0.04019598
	hsa-miR-155	2.025291111	0.00719928

Table. Some microRNAs which will control Th17 cell differentiations.

3. Result

Some microRNAs inhibited disease situation of arthritis. On the other hand, some microRNAs aggravated disease situation.

4. For Application

It is necessary to ensure safety and efficacy for human use.

Competitive Advantages

MicroRNA has a potential to be a new tool to treat arthritis including rheumatoid arthritis.

Patent/Journal/Award

URL

Life Science

Regulation of Gastrointestinal Function by Food Factors

Keywords Polyphenols, Flavonoids, Oligosaccharides, Gastrointestinal Function

Takuya SUZUKI

Department Graduate School of Biosphere Science
Title Associate Professor / Lecturer

E-mail takuya@hiroshima-u.ac.jp
Field Agricultural Chemistry, Food Science

Outline

1. Background

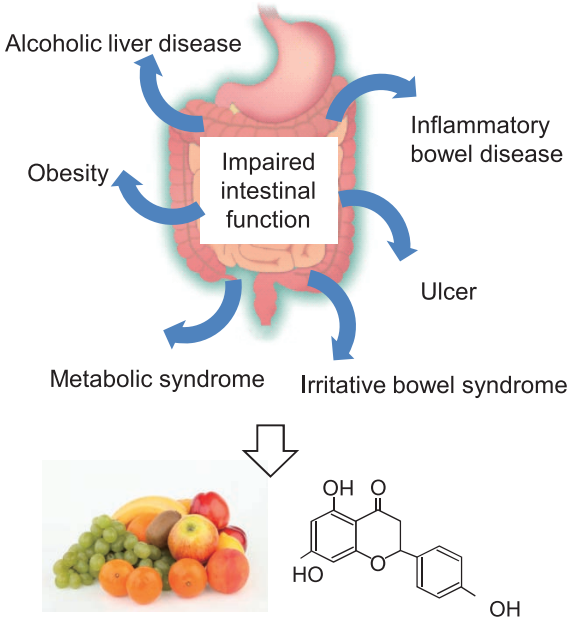
Recent studies demonstrate that the intestinal barrier defect is involved in the pathogenesis of various diseases, such as inflammatory bowel disease, ulcer, irritative bowel syndrome, obesity, metabolic syndrome, and alcoholic liver disease. Therefore, the regulation and protection of intestinal barrier integrity by food factors could be a therapeutic tool for the diseases mentioned above.

2. Research Summary

The potential of polyphenols, which distribute throughout the plant kingdom, to regulate the intestinal barrier integrity and restore the intestinal inflammation was investigated using intestinal cells and a murine model of colitis.

3. Result

Among several polyphenols, naringenin, quercetin, myricetin, kaempferol, hesperetin, and curcumin have promotive effects on the intestinal barrier integrity. Further, naringenin, quercetin, hesperetin and curcumin restore the intestinal inflammation as well as barrier impairment in the murine model of colitis.



Prevention and improvement by food factors
Creation of novel functional foods

4. For Application

A large number of people often feel something wrong with the gut. Under these conditions, they may suffer the increased intestinal permeability and inflammation, resulting in various intestinal and systemic diseases. Our findings can lead to novel functional foods and contribute to the preservation and improvement of health.

Competitive Advantages

At the present moment, no functional food to protect and promote the intestinal barrier function is commercially available. This is a big advantage to start business. In addition, many polyphenols are known to be safe for human consumption and can be easily utilized in functional foods.

Patent/Journal/Award

Suzuki, T. et al. J Nutr 2011, 141, 87–94.
Suzuki, T. et al. J Nutr 2009, 139, 965–74.
Suzuki, T. et al. J Nutr Biochem 2011, 22, 401–8.

URL URL http://home.hiroshima-u.ac.jp/douri/Suzuki group/Top page_en.html

Life Science

Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency: Functional Analysis of Mutant Enzymes Found in Japanese Patients

Keywords Fatty Acid Oxidation Disorders, Sudden Infant Death, Newborn Screening, Tandem Mass Spectrometry

Go TAJIMA

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail ugovan@hiroshima-u.ac.jp

Field Clinical Internal Medicine (Pediatrics)

Outline

1. Background

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an inborn error of fatty acid oxidation system, which mainly causes acute encephalopathy or sudden death to infants and young children, triggered by insufficient oral intake of carbohydrates. While tandem mass spectrometry-based newborn screening (NBS) is being implemented nationwide, it is essential to establish a prompt inspection system which supports confirmatory diagnosis of positive cases and evaluation of the seriousness of the enzymatic defects in order to truly improve child health.

2. Research Summary

Since 2001, we have measured MCAD activity in lymphocytes of peripheral blood using HPLC, on cases of NBS- positive or those suspected after clinical onset in various regions within Japan. We also carried out gene analysis by direct sequencing method on cases of lower activity. Mutation spectrum of Japanese patients is considerably different from that of European/American Caucasians.

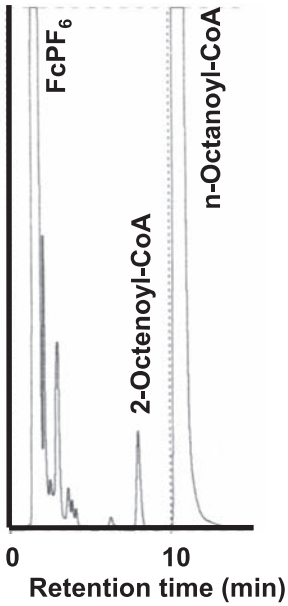
It seemed necessary to evaluate functional disorder of each mutant enzyme in order to detect patients with true risks of sudden development of clinical symptoms and provide appropriate treatment. As a method, we prepared overexpression system of mutant MCAD enzymes and measured their activity in the same way as that for lymphocytes.

HPLC chromatogram of MCAD reaction by lymphocytes:

n-Octanoyl-CoA and artificial electron acceptor $FcPF_6$ are mixed with crude lysate of lymphocytes. After incubation, the supernatant is analyzed by reverse phase HPLC, and the product is quantified by 260nm UV absorption.

↓

After about 8 minutes of retention, reaction product 2-octenoyl-CoA can be clearly separated and quantified.



3. Results

Through the last decade, more than 30 cases of MCAD deficiency were found in Japan, and approximately two thirds of them were confirmed by our enzymatic diagnosis method. Not a few of NBS-positive cases kept considerably high levels of residual activity in lymphocytes and, by using overexpression system, mutant enzymes detected in such cases showed activities as high as 50 to 100% of wild type enzyme.

4. For Application

The present technology is already in state of clinical application. Considering that NBS will be continued in a long-term from now on, it is desirable to carry out enzyme measurement and gene analysis under health insurance, and to carry out a laboratory study on functional analysis of mutant enzymes.

Competitive Advantages

The major characteristic of our enzymatic diagnosis method is simple in procedure and clearly identifies patients from the normal, and will also identify many carriers, compared with various existing methods reported. HPLC is an analytical instrument of general purpose, and seems to be owned by many general laboratories. Therefore the present technology can be easily introduced by testing sites of many regions in Japan.

Patent/Journal/Award

Tajima G, Sakura N, et al: J Chromatogr B Analyt Technol Biomed Life Sci 823: 122–130, 2005.

Japanese Society for Inherited Metabolic Diseases Fellowship Award 2009

URL http://seeds.hiroshima-u.ac.jp/soran/e338e8c/r.html

Life Science

Indigenous Symbiotic Environmental Bacteria in the Intestinal Mucosa Drive the Quiescent Mucosal Immune Responses

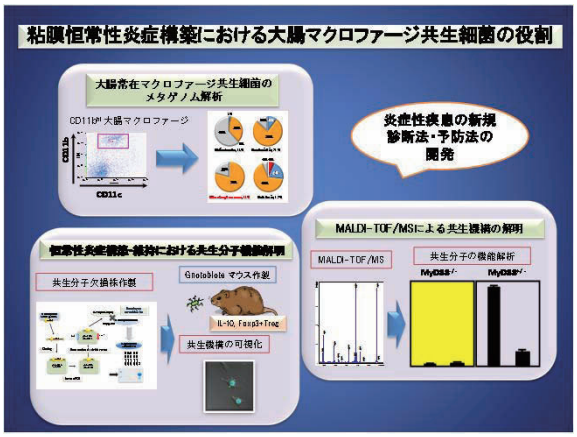
Keywords Symbiosis, Commensal Bacteria, Mucosal Homeostasis, Immune Regulation

Ichiro TAKAHASHI
Department Institute of Biomedical & Health Sciences
Title Professor
E-mail snatum@hiroshima-u.ac.jp
Field Mucosal Immunity

Outline

1. Background

Several gut commensal bacteria such as segmented filamentous bacteria, polysaccharide antigen A-producing *Bacteroides fragilis*, and the cocktail of *Clostridium* species sustain particular Th cell differentiation. Furthermore, our previous study demonstrated that indigenous *Alcaligenes* species inhabit mammalian gut-associated lymphoid tissues and share a mucosal IgA-mediated symbiosis. However, it remains to be elucidated whether or not particular commensal bacteria are selectively resident in mononuclear phagocytes in the colon, leading to particular Th cell responses.



2. Research Summary

We analyzed the composition of microbiota resident in colonic CD11b^{+}phagocytes by 16S ribosomal RNA analysis and studied the in vivo and in vitro immunobiological activity of the bacteria.

3. Result

Our results showed that defined aerobic *Proteobacteria* such as *Ralstonia* and *Stenotrophomonas* were exclusively colonized in the colonic CD11b^{+}phagocytes. We next observed that a strain of *S. maltophilia* strongly induced IL-10 production in RAW cells. A 25 kDa secreted protein (a product of the s*mlt2713* gene) isolated from *S. maltophilia* exhibited the identical activities. By using several TLR-related molecule deficient mice, we observed the IL-10 production was MyD88 dependent. Finally, we noticed that colonization of germ-free mice with *S. maltophilia* induced strong IL-10 productions as well as Foxp^{3+}Treg cells in the colon. Our data indicate defined environmental bacteria such as aerobic *S. maltophilia* resident in the colonic phagocytes make fundamental immunosymbiotic properties in the gastrointestinal tissues.

Patent/Journal/Award

"The gut-resident commensal bacteria derived polypeptide and the method of its production" (#2011-033867) Hiroshima University, The University of Tokyo, Tokyo Medical and Dental University, and Kitasato University. February 18, 2011.

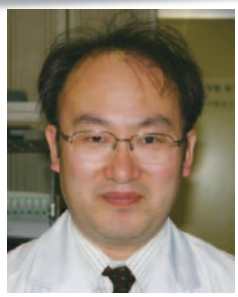
Toubou H, Goto Y, Kurashima Y, Kiyono H, Maruyama F, Nakagawa I, Kurushima J, Abe A, Hayashi I, Takahashi I. Indigenous environmental bacteria involve the creation of mucosal homeostasis. The 40th Annual Meeting of Japanese Society of Immunology. Chiba, Japan. November 28, 2011.

URL http://www.mucosal-hiroshima.jp

Life Science

Study on Target Gene of miRNA miR224 Which is Overexpressed in Hepatocellular Carcinoma

Keywords Hepatocellular Carcinoma, miRNA



Shoichi TAKAHASHI

Department Hiroshima University Hospital
Title Assistant Professor
E-mail shoichit@hiroshima-u.ac.jp
Field Hepatology

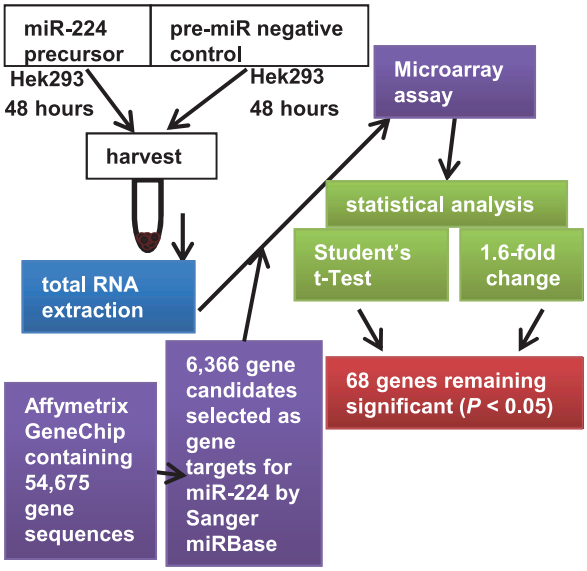
Outline

1. Background

It has been discovered that microRNA (miRNA), which is copied from non-coding genomic region, plays an important role in living organism. In present study, the role of miRNA, in development and growth of hepatocellular carcinoma, was considered by investigating overexpressed miRNA and identifying its target gene.

2. Research Summary

1) Amplify miRNA extracted from cancerous tissues and adjacent non-cancerous tissues of hepatic resection, using real-time PCR, and identify miRNA which is overexpressed in cancerous tissue. 2) Introduce miRNA that is overexpressed in liver cancer into normal cell strain, and among the genes whose expression level changes, those genes which can be directly joined by the subject miRNA are considered with sequencing analysis and cDNA microarray. 3) Verify by RT-PCR whether the subject miRNA actually controls the candidate gene extracted by cDNA microarray. Also consider the variation in protein expression. 4) Consider whether the same results can be obtained in cancerous tissues and adjacent non-cancerous tissues of hepatic resection as in the cultured tissue.



3. Result

High expression of miR-224 was confirmed in cancerous tissues of hepatic resection. In addition, in cDNA microarray using cultured cells, under the forced miR-224 expression, decreased expression of CDC42, E-cadherin, and PAK2, and increased expression of BCL-2 and MAPK were observed. Similar observation was also obtained from cancerous tissues of hepatic resection. It is suggested that in liver cancer with higher miR-224 expression, the risks of multiple organ metastasis increase owing to attenuation of adhesion factor, and survival signal is enhanced.

4. For Application

Utilize as a tumor marker, by measuring miR-224 in blood (in blood exosome) of chronic liver disease patients, and estimating the development of cancer that cannot be identified by diagnostic imaging.

Competitive Advantages

There are many studies on expression of microRNA in cancer cells, however, not many consider it in combination with target sequence and cDNA microarray. The present study will allow to identify the gene which miRNA directly controls.

Patent/Journal/Award

Under review.

URL

Life Science

Transport of Insulin and its Regulation in Alveolar Epithelial Cells

Keywords Insulin, Alveolar Epithelial Cells, Endocytosis

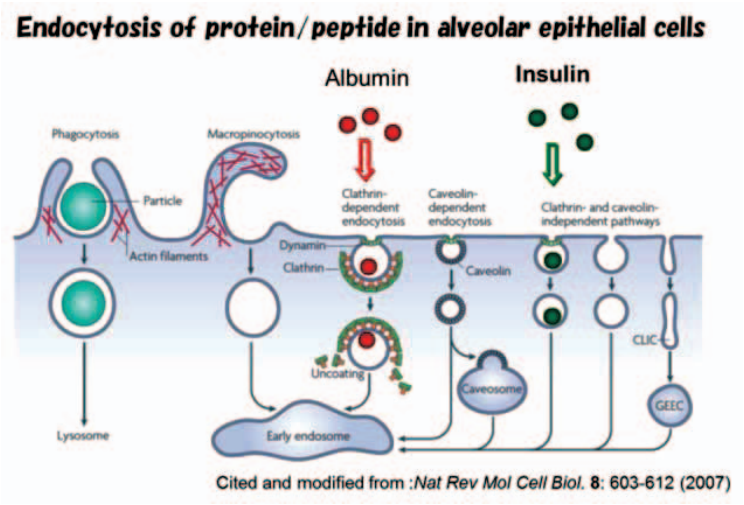
Mikihisa TAKANO
Department Institute of Biomedical & Health Sciences
Title Professor
E-mail takanom@hiroshima-u.ac.jp Field Pharmaceutical Sciences

Outline

1. Background

The lung has attracted a great deal of interest as an alternative administration route for protein and peptide drugs. However, the information concerning the handling of proteins and peptides in alveolar epithelial cells is still lacking.

The objective of this study is to clarify the mechanisms of insulin transport in alveolar epithelial cells, and to establish the strategy to enhance insulin absorption from the lung.



2. Research Summary

Transport mechanisms of FITC-insulin were examined in cultured alveolar epithelia cell line RLE-6TN.

In addition, the effects of poly(amino acid)s such as poly-L-ornithine (PLO) on insulin uptake were examined in RLE-6TN cells.

3. Result

1) Insulin is taken up through endocytosis in RLE-6TN cells, and after the endocytosis, the intracellular insulin is partly degraded in lysosomes and partly transported to the basal side. Insulin receptor, but not megalin, may be involved at least partly in insulin endocytosis in RLE-6TN cells.
2) Co-administration of poly(amino acid)s such as PLO is a useful strategy for enhancing insulin uptake by alveolar epithelial cells and subsequent absorption from the lung.

4. For Application

Pharmaceutical Industries/ Development of inhaled drugs

The safety of poly(amino acid)s should be confirmed further.

Competitive Advantages

Our strategy is easier than the method that needs covalent modification of insulin, and may be widely applicable.

Patent/Journal/Award

Oda, K., Yumoto, R., Nagai, J., Katayama, H. and Takano, M.: Mechanism underlying insulin uptake in alveolar epithelial cell line RLE-6TN. Eur. J. Pharmacol., 672, 62–69 (2011)

URL

Life Science

Establishment of Jaw Bone Reconstruction Using High Functional Material for Restoration of the Ideal Jaw Form and the Occlusal Function

Keywords Biocompatible Material, Functional Ceramics, Jaw Bone Reconstruction

Masaaki TAKECHI

Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail takechi@hiroshima-u.ac.jp
Field Oral Surgery, Oral and Maxillofacial Reconstructive Surgery, Tissue Engineering

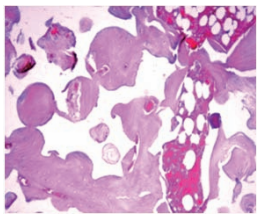
Outline

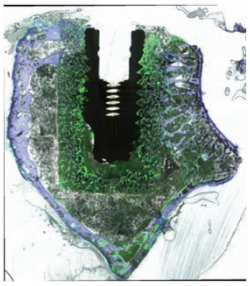
1. Background

The goal of the reconstructive surgery is to restore the ideal jaw form and the occlusal function. The aim of this study is to establish of jaw bone reconstruction using high functional material for restoration of the ideal jaw form and the occlusal function.

2. Research Summary

We evaluated the bone regeneration of osteoblasts derived from tibia of rats and human jaw bone cultured on interconnected porous hydroxyapatite ceramics (IP-CHA) in vitro and in vivo. Also, the tissue responses to the composite IP-CHA and dental implant was evaluated by implanting into bone defects of rabbit femur.





3. Result

In the evaluation of bone regeneration IP-CHA by using osteoblasts of rats and human, IP-CHA promoted differentiation of osteoblasts into mature osteoblasts. Then, we found that the ability of osteoblast proliferation and calcification in IP-CHA. In the case of IP-CHA/osteoblast composite group, more abundant new bone was formed not only in the surface area, but also in the inner pore areas compared with IP-CHA only group after implantation. In histological experiment of the composite IP-CHA and dental implant, newly formed bone was observed around the dental implant and the implant stability quatient (ISQ) values was increasing gradually after implantation. From these results, it was found that good osseointegration was obtained functionally and histologically in the case of composite IP-CHA and dental implant.

4. For Application

Because IP-CHA come onto the market at present, it has been basically guaranteed its safety to the quality. In future, If IP-CHA block will be obtained an authorization of the pharmaceutical affairs law from Japanese Ministry of Health, Labor and Welfare, IP-CHA can be a useful biomaterials for tissue engineering not only in dental field but also in whole medical field.

Competitive Advantages

The final object of this study is to recover the characteristic ideal jaw formation and the occlusional function in each patients have bone defects. IP-CHA is customized by CAD/CAM technique to construct the patient's original jaw bone. Therefore, if this custom-made regenerative medicine will be established in future by this research, it is very useful in bone regeneration treatment.

Patent/Journal/Award

Hiraoka, M, Takechi, M.et.al: Archives of Bioceramics Research
Shigeishi, H, Takechi, M. et.al: Dent. Mater. J

URL

Life Science

Survey on Male Dental Hygienists

Keywords Dental Hygienist, Male, Gender, Working Condition

Toshinobu TAKEMOTO
Department Institute of Biomedical & Health Sciences
Title Professor
E-mail takefn@hiroshima-u.ac.jp
Field Social Dentistry

Outline

1. Background

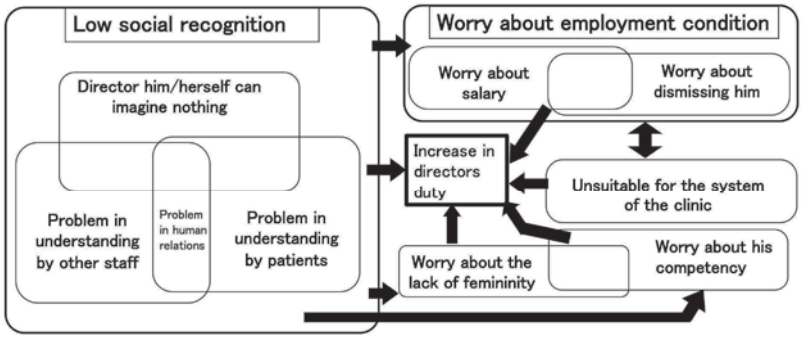
With the advancement of dental hygienists education, the number of male dental hygienist has been gradually increasing. On the other hand, by social cognition, dental hygienist is a profession of women, hence, there remains a problem in terms of gender. In this study, we made a research on male dental hygienist.

2. Research Summary

Survey was performed by mail to the director of private dental clinics in Hiroshima prefecture, Japan. There were total 118 responses. Analysis was done using spreadsheet software for numerical data, and KJ-technique was also performed against qualitative data.

3. Result

The reasons for desiring to employ male dental hygienists were mainly the expectations of long term employment and professionalism. The reasons for not desiring to employ them were mainly the problem of salary and worry about employing them. The basic problem in the employment of male dental hygienists was understood to be the low social recognition about them. We have to improve the employment condition of dental hygienists overall and to make male dental hygienists socially “well-recognized”.



Anxiety in employing male dental hygienist (analyzed according to KJ-technique)

4. For Application

We hope there will be some improvement in the employment condition of dental hygienists according to our research results.

Competitive Advantages

This is the first report for the survey on male dental hygienists.

Patent/Journal/Award

Journal: [Investigation on the recognition about male dental hygienists by dentists-Analysis of cross sectional research to director of private dental clinic in Hiroshima prefecture][ja]: J Hiroshima Univ Dent Soc, 43(2), 98–105, 2011.

URL http://www.hiroshima-u.ac.jp/en/bimes

Life Science

Integrative Analyses of Neuropsychiatric Diseases

Keywords Autism, Mood Disorders, ALS, Circadian Rhythm, Spine, RNA Binding Protein

Toru TAKUMI

Department Institute of Biomedical & Health Sciences

Title Professor

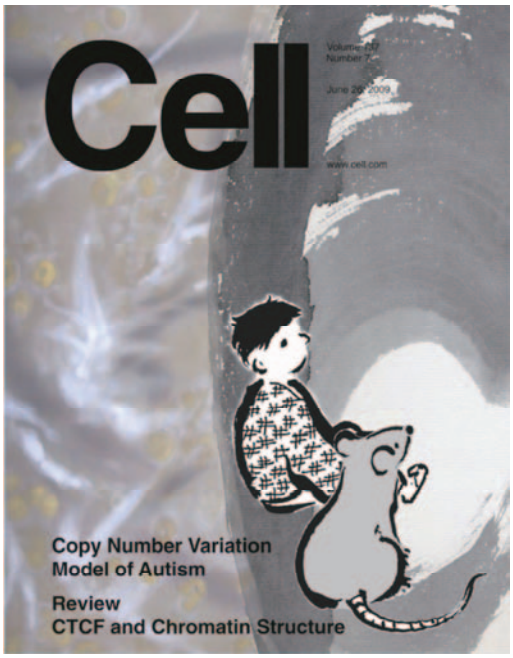
E-mail takumi@hiroshima-u.ac.jp

Field Molecular Neuroscience

Outline

1. Background

We are interested in molecular bases of broad neuropsychiatric diseases, including autism, depression and ALS.



2. Research Summary

(1) Mouse models of autism

(2) Molecular link between circadian clocks and mood

(3) RNA processing and neural degeneration

(4) Integrative approaches to understand circadian rhythms

(5) Molecular cell biology of spines

3. Result

The humanoid mouse model of autism

4. For Application

Competitive Advantages

Our mouse model of 15q duplication has been generated by chromosome-engineering technique. The mice contain not only face validity but also construct validity.

Patent/Journal/Award

A chromosome-engineered mice of 15q duplication/Nakatani et al, Cell, 2009.

Ervin von Baerlz Prize (2009).

URL http://home.hiroshima-u.ac.jp/anatomy2/index.html

Life Science

Molecular Biology of the Age-related Hearing Loss and Vertigo

Keywords Inner Ear, Age-related Hearing Loss, Radical Scavenger, Treatment

Masaya TAKUMIDA

Department Hiroshima University Hospital
Title Associate Professor / Lecturer
E-mail masati@hiroshima-u.ac.jp
Field Otorhinolaryngology

Outline

1. Background

Hearing loss and dizziness due to aging have become major problems, which cause a significant impact on QOL of the elderly, and induce a problem in the social economy. In addition, it has been reported that dizziness in the elderly increases every year since more than 20 years ago already.

Basic research
↓
By using old mice the factor of age-related hearing loss should be examined.

Clinical application
Treatment to the elderly with age-related hearing loss

2. Research Summary

Our research results showed that free radicals play an important role for the inner ear disorders. Especially in the elderly, radical scavenging capacity in the inner ear is reduced. The treatment with radical scavenger may reduce the inner ear damage, i.e. Meniere's disease, cisplatinum ototoxicity, age-related hearing loss, etc.

3. Result

In the animal experiments, radical scavenger may reduce the damage in almost all types of inner ear disorders. Clinical application of radical scavengers may improve the hearing in patients with age-related hearing loss, Meniere's disease, and Cisplatinum ototoxicity.

4. For Application

Development of new type of radical scavengers.
Application of supplements (vitamin C, E, alpha lipoic acid, coenzyme Q, astaxamtin, etc.)

Competitive Advantages

In this field our group first discovered the efficacy of radical scavengers in the inner ear disease. Our research may develop a new treatment of inner ear disease.

Patent/Journal/Award

Takumida M, Anniko M: Radical scavengers for elderly patients with age-related hearing loss. Acta Otolaryngol 129: 36–44, 200.

URL

Life Science

Analysis of Chromosome Engineered Mouse Model for Autism

Keywords Autism, Serotonin, 15q11-13, Mouse Model

Kota TAMADA

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail ktamada@hiroshima-u.ac.jp

Field Basic Medical Sciences, Basic Biology

Outline

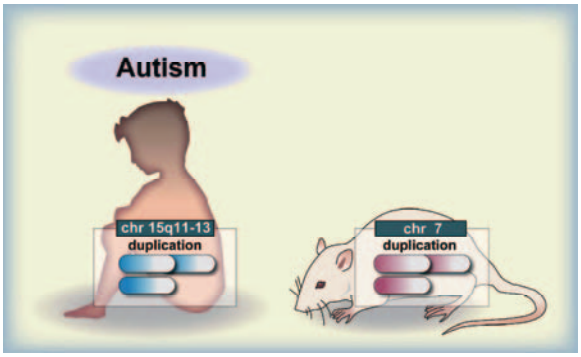
1. Background

Recent reports using high-resolution genetic techniques revealed that a de novo copy number variations (CNVs) has a significant risk factor for autism. Although many CNVs have been reported, the duplicaiton of human chromosome 15q11–13 is the most frequent chromosomal arrangement, found in 1–4% of autism.

2. Research Summary

We focused on the chromosome 15q11–13 region and succeeded to make a mouse model for its duplication. Using many techniques, we analyze this mouse at molecular, cellular, tissue or behavior level.

Chromosome engineered mouse model for autism



3. Result

This mouse model for autism showed autistic like behaviors and also have decreased locomotor activity in the novel environmental condition. Furthermore, this mouse have decreased level of serotonin in its brain especially manifested in developmental stages.

4. For Application

Further analysis of this mouse leads to understanding of the mechanism or generating the drug for autism.

Competitive Advantages

There has been never reported about autism mouse model with CNVs in autism until our study.

And also this mouse have recapitulate not only the symptoms but also molecular mechanisms, like decreased serotonin capacity in brain.

Patent/Journal/Award

2009 Cell vol. 137, pp1235–1246.

2010 PLoS ONE vol. 5, e15126.

URL http://home.hiroshima-u.ac.jp/anatomy2/index.html

Life Science

Study on Therapeutic Strategy for Colorectal Submucosal Carcinoma after Endoscopic Treatment

Keywords Colorectal Submucosal Carcinoma, SM Cancer, Endoscopic Treatment

Shinji TANAKA

Department Hiroshima University Hospital
Title Professor and Director

E-mail colon@hiroshima-u.ac.jp
Field Gastroenterology and Endoscopy

Outline

1. Background

Colorectal carcinoma (CRC) with SM invasion shows lymph node (LN) metastasis in about 10%. After endoscopic resection for SM-CRC we have to determine the necessity of additional surgery with LN dissection. In this situation adequate indicator for LN metastasis has been required.

2. Research Summary

Using clinical cases of SM-CRC, we examine histological risk factors for LN metastasis and establish the concrete condition to reduce the no meaning additional surgery for LN negative cases after endoscopic resection.

3. Result

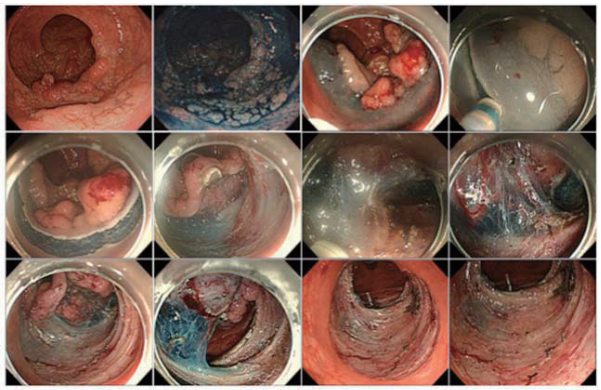
SM-CRC with both differentiated histologic type, negative vessel involvement and low grade budding has metastatic potential in only 1.2% irrespective of the SM invasion depth.

4. For Application

Multicenter study using a larger amount of cases is necessary to confirm our results. In order to keep the accuracy of histologic diagnosis in each hospital, we expect the development of computer aided diagnosis (CAD) system.

Rate of lymph node metastasis in colorectal SM carcinoma with differentiated histology, no vessel involvement and budding low grade in each SM invasion depth

SM invasion depth	Rate of lymph node metastasis, %		95% CI (%)
SM<1000μm	0	(0/114)	0-2.59
SM<1500μm	0	(0/149)	0-1.99
SM<1800μm	0	(0/158)	0-1.88
SM<2000μm	1.22	(2/164)	0.15-4.34
SM<3000μm	1.56	(3/192)	0.53-5.00
SM<4000μm	1.41	(3/213)	0.29-4.06
SM<5000μm	1.33	(3/226)	0.27-3.83
Over all cases	1.20	(3/249)	0.25-3.48



A case with SM-CRC treated by endoscopic resection

Competitive Advantages

If we can judge the existence of LN metastasis after endoscopic treatment (non-invasive treatment in comparison with surgery or chemotherapy), we are able to reduce the number of no meaning additional surgery for SM-CRC without LN metastasis. In the near future we are planning the induction of molecular/biologic markers predict LN metastasis more in detail. Now this research is ongoing.

Patent/Journal/Award

Nakadoi K, **Tanaka S**, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol 2012, in press.

URL http://home.hiroshima-u.ac.jp/endosc/

Life Science

Exploitation of MICA Gene Polymorphism for Development of Personalized Medicine in Oral Cancer Patients

Keywords Cancer, Immunotherapy, Personalized Medicine, NK Cells, Cell Therapy

Ryouji TANI

Department Hiroshima University Hospital
Title Assistant Professor
E-mail ryouji@hiroshima-u.ac.jp
Field Oral Surgey

Outline

1. Background

In order to acquire the high outcome of oral cancer treatment, I exploit MICA gene polymorphism for development of personalized medicine for oral cancer patients.

2. Research Summary

The MICA gene has a triplet repeat (GCT) polymorphism in the transmembrane domain, and relevance with the disease susceptibility of Type Ⅰ-DM. To evaluate the possible association of MICA gene polymorphism with the risk for oral squamous cell carcinoma (OSCC), we analysed MICA polymorphism in cases with OSCC by direct sequencing and fragment analysis.

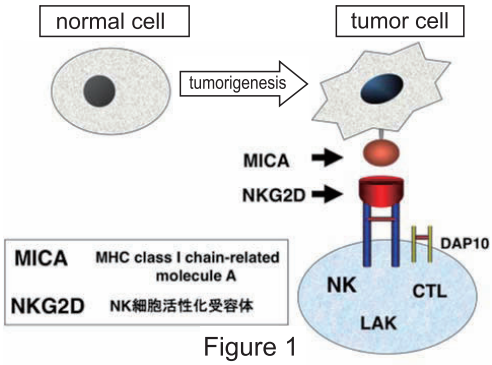


Figure 1

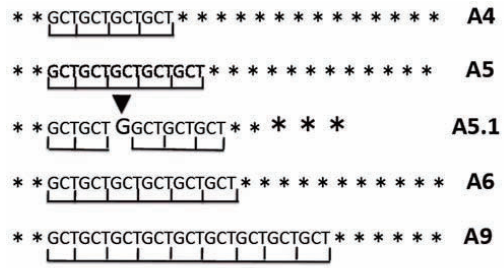


Figure 2

3. Result

Five distinct MICA alleles A4, A5, A6, A9, and A5.1 were studied. MICA 5.1 variant gene contains a fournucleotide insertion that causes a stop codon in the transmembrane region. In addition, as an sMICA has been considered to cause the down regulation of NKG2D resulted in suppression of NK cells and antigen-specific effector T cells. As the result, we have found that the phenotype frequency of allele 5.1 of MICA and the sMICA levels in subjects with OSCC were significantly higher than those in controls.

4. For Application

Cancer treatment and development of molecular tumor marker

Competitive Advantages

MICA will be useful for a new molecular target in oral cancer.

Patent/Journal/Award

URL

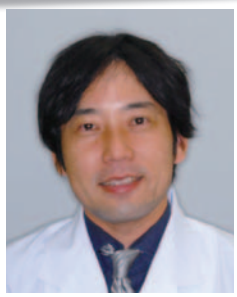
Life Science

A New Technology for Treatment of Dental Caries- Regeneration of Tooth Enamel with Amelogenin

Keywords Dental Caries, Enamel Matrix Protein, Amelogenin, Regeneration

Kotaro TANIMOTO

Department Hiroshima University Hospital
Title Associate Professor / Lecturer
E-mail tkotaro@hiroshima-u.ac.jp
Field Orthodontics



Outline

1. Background

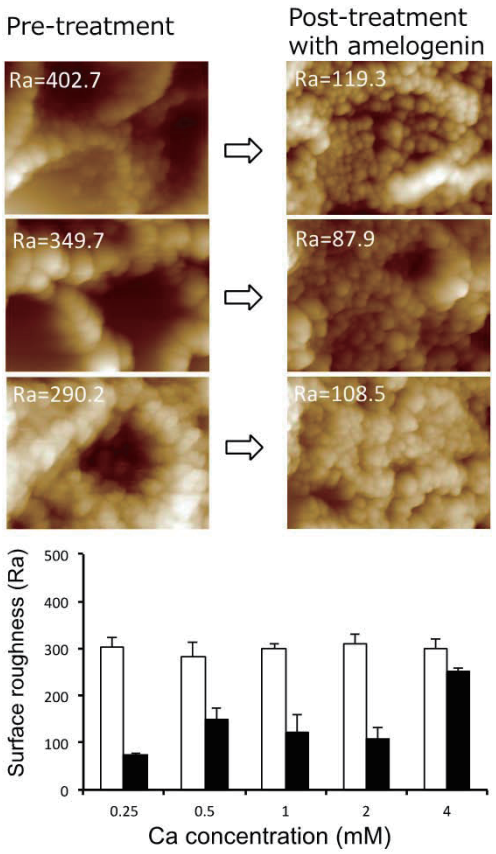
The enamel mineral tissue is developed from a layer of soft protein matrix secreted by a layer of epithelial cells, the ameloblasts. The dominant enamel matrix protein is amelogenin, and has been considered to play an essential role in the control and modulation of enamel crystal growth. The purpose of this study was to investigate the *in vitro* amelogenin-guided induction of hydroxyapatite crystal on the surface of tooth enamel.

2. Research Summary

The surface of extracted teeth was treated with solution containing calcium nitrate, potassium phosphate, and recombinant human amelogenin for 16 hr. The crystal formation on tooth enamel surface was evaluated using digital binocular wide-field dissecting microscope and atomic force microscope (AFM). Roughness (Ra) of enamel surface before and after the treatment was quantified using AFM and VN viewer software.

3. Result

The crystal formation on the surface of tooth enamel was shown after the treatment with amelogenin, whereas no crystal induction was observed in the control group treated with solution not containing amelogenin. The surface roughness (Ra) was decreased significantly by the treatment with amelogenin as compared to the control group.



4. For Application

This study is designed to establish a basic technology for regeneration of tooth enamel with early caries. In case this technique is put to practical use, aesthetic regeneration of tooth enamel will be accomplished without tooth preparation and filling with artificial materials. Establishment of a method for purification of large amount of amelogenin, and the examination to verify the safety is needed in future study.

Competitive Advantages

Generally, initial caries is treated by application of fluoride and plaque control to expect natural recalcification, however, this method cannot ensure the recalcification. The method in this study has an advantage over previous treatment methods in terms of the positive induction of recalcification in tooth enamel with initial caries.

Patent/Journal/Award

Japanese Patent Pending: 2011–027923, Solution and kit for regeneration of tooth enamel (February 10, 2011)

URL

Life Science

Direct Vasodilation by Transdermal Administration of Nitroglycerin: Nitroglycerin Skin Spray for Premedication before Artery Puncture

Keywords Nitroglycerin, Premedication before Artery Puncture

Keizo TANITAME

Department Hiroshima University Hospital

Title Assistant Professor

E-mail tntrad@ms1.megaegg.ne.jp

Field Medicine, Radiology

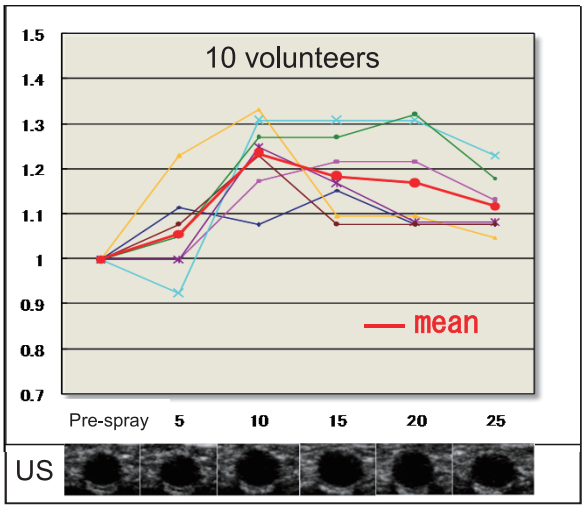
Outline

1. Background

Nitroglycerin (NTG) solution placed on the skin surface infiltrates into subcutaneous tissue and directly dilates subcutaneous vessels. As approaches using the brachial or radial artery carry a relatively high risk of procedural failure due to those small caliber, the transdermal administration of NTG before arterial puncture may improve the puncture success rate.

2. Research Summary

For evaluating the vasodilation effect of NTG skin spray on brachial arteries, we recruited 10 healthy volunteers and sprayed their skin above right or left brachial artery with a solution containing 0.3 mg NTG or above right brachial artery with physiological saline on different days and in random order. The cross-sectional area of right brachial artery before and at 5-min intervals for up to 25 min after spraying was ultrasonographically measured and calculated the incremental rate of the area.



3. Result

The average vasodilation rate after spraying with NTG above right brachial arteries of 10 volunteers was 16.4% at 5 min, 23.6% at 10 min, 19.6% at 15 min, and 16.5% at 20 min; spraying with NTG above the left brachial artery or with physiological saline alone elicited few changes. The vasodilation rate 10 min after spraying with NTG above the right brachial artery was significantly higher than control groups ($P < 0.001$). There was little change in the blood pressure and pulse rate after NTG skin spray application and the participants experienced no side effects other than slight heating of the skin sprayed with NTG.

4. For Application

The transdermal NTG administration represents a non-invasive technique that dilates superficial arteries effectively. This technique may be a good premedication before artery puncture. In patients where the NTG skin application elicits major side effects, residual amounts can be easily wiped off the skin surface. The transdermal delivery of NTG by spraying the skin above the target vessel is safer than its systemic administration or topical subcutaneous injection.

Competitive Advantages

NTG skin application before artery puncture may be a novel premedication method. Our study has some limitations: First, the vasodilation effects of the NTG skin application in patients with diseases such as arteriosclerosis and diabetes mellitus must be investigated. Second, this preliminary study examined the dilation effects of transdermally-administered NTG on the brachial artery ultrasonographically. Randomized clinical trials using diagnostic and interventional angiography are needed to determine whether the transdermal administration of NTG facilitates catheterization of superficial arteries.

Patent/Journal/Award

Keizo Tanitame et al. Direct vasodilation by transdermal administration of nitroglycerin: preliminary, randomized, placebo-controlled trial of nitroglycerin skin spray for premedication before artery puncture. JJR 2012, Epub, ahead of print.

URL http://www.springer.com/medicine/radiology/11604

Life Science

Development of a Functional Food with an Aim to Enhance Bone Volume

Keywords Bone Volume, Bone Mineral Density, CPP, Black Bean

Kazuo TANNE

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail tanne@hiroshima-u.ac.jp

Field Dentistry (Pediatric Dentistry/Orthodontics)

Outline

1. Background

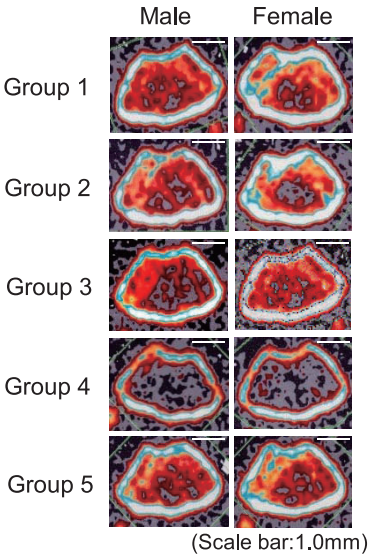
Osteoporosis with a decrease in bone volume and density as a principal symptom generates a reduction in QOL through bone fracture and the resultant locomotive syndrome. In order to solve such problems, we examined the effects of a functional food with use of orchiectomy (ORX) / ovariectomy (OVX) mice developed in our laboratory.

2. Research Summary

Normal and ORX/OVX mice were fed on normal and low calcium foods (NCF, LCF) and special calcium food (SCF) supplemented with casein phosphopeptide (CPP) and black bean. Bone volume and mineral density were analyzed by use of a peripheral quantitative computed tomography (pQCT).

Control: group 1 Cont. +NCF(18w) normal calcium level
group 2 Cont. +LCF(18w) low calcium level
Experimental group 3 Cont. +LCF(6w)→SCF(12w)
group 4 ORX or OVX +LCF(18w) simulated osteoporosis
group 5 ORX or OVX +LCF(6w)→SCF(12w)

pQCT images of cross-sectioned femurs



(Scale bar:1.0mm)

3. Result

Mice in group 5 exhibited significantly greater values of both bone volume and mineral density when compared to those in groups 1, 2 and 4. From these findings, it is demonstrated that the functional food is available for the enhancement of bone volume in subjects with reduced bone volume and/ of mineral density.

4. For Application

It is highly anticipated for the elderly of over 40-year-old, post-menopause women in particular, to enhance bone volume and/or density.

Competitive Advantages

CPP and Ca and Mg with a ratio of 2:1 are added to black bean in this functional food, therefore, it is confirmed that this food has an additional effect to enhance bone volume in the symptomatic subjects without producing any significant side effects.

Patent/Journal/Award

Ohtani J. *et al., Nutrition. J.* 8, doi: 10. 1186/1475–2891–8–30.

URL

Life Science

Molecular and Cellular Target Therapy for Hepatic Stellate Cell Using Rho Kinase Inhibitor

Keywords Rho kinase, Hepatic Stellate Cell, Liposome, Vitamin A

Hirotaka TASHIRO

Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail htashiro@hiroshima-u.ac.jp
Field Gastroenterological Surgery

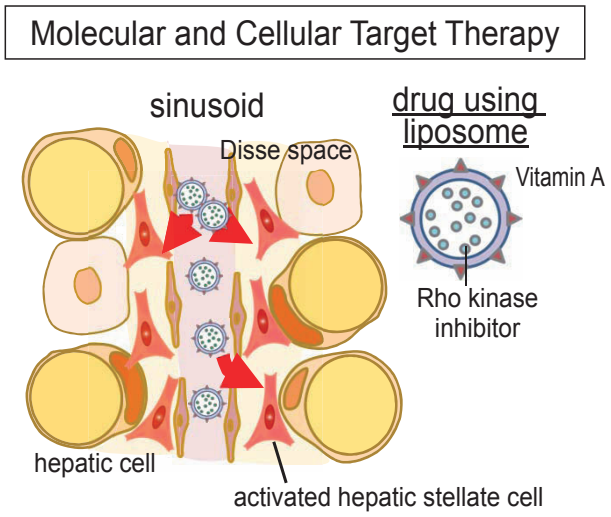
Outline

1. Background

We have reported that activation of Rho/Rho-kinase signaling in hepatic stellate cells is associated with an increased susceptibility to ischemia-reperfusion injury. An Rho-kinase inhibitor attenuated the activation of hepatic stellate cells and improved ischemia-reperfusion injury.

2. Research Summary

We have developed the vitamin A-coupled liposomes containing Rho kinase inhibitor. We have also investigated whether the loposomes attenuate ischemia-reperfusion injury in rats, and examined to what extent the liposomes attenuate the deleterious effects of Rho kinase inhibitor such as hypotension and renal dysfunction.



3. Result

The liposomes have ameliorated the ischemia-reperfusion injuries at the dose of one-hundreds compared with alone Rho kinase inhibitor, with attenuating the side effects such as a hypotension.

4. For Application

We are planning to examine if and to what extent Rho kinase inhibitor is specifically delivered to hepatic stellate cells. These liposomes are expected to be used as drug for portal hypertension and hepatic fibrosis.

Competitive Advantages

Development of drug delivery systems: production of liposomes carrying Rho kinase inhibitor to hepatic stellate cells as target cells.

Patent/Journal/Award

Kuroda S, Tashiro H, Igarashi Y, Tanimoto Y, Nambu J, Oshita A, Kobayashi T, Amano H, Tanaka Y, Ohdan H. Rho inhibitor prevents ischemia-reperfusion injury in the rat steatotic liver. J Hepatology 2012; 56: 146–152.

URL

Life Science

Developing the Culture Technology of Pituitary Stem Cell in the Zero Gravity Environment

Keywords Artificial Pituitary Gland, Zero Gravity, Stem Cell

Atsushi TOMINAGA

Department Institute of Biomedical & Health Sciences

Title Associate Professor

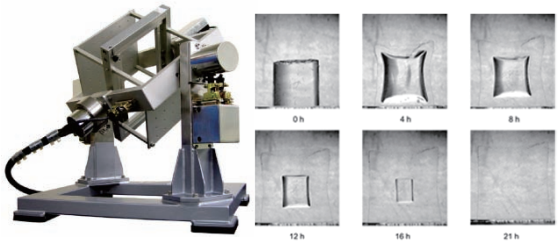
E-mail atom@hiroshima-u.ac.jp

Field Neurosurgery

Outline

1. Background

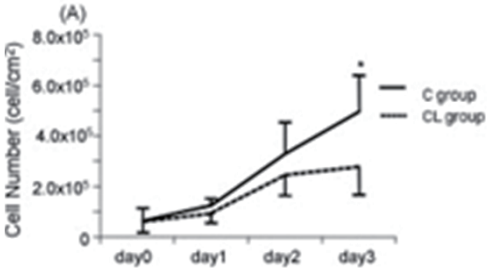
We have developed the gel capsule for artificial pituitary gland in cooperation with the Faculty of Engineering . The pituitary stem cell is needed for artificial pituitary gland, but we have various hurdles to culture it. It is reported that the artificial zero gravity equipment is able to culture undifferenciated stem cell densly.



2. Research Summary

We make zero gravity environment using zero gravity equipment and culture the pituitary stem cell efficiently in that environment.

We analyze the role of stem cell in the pituitary gland, and develop the artificial pituitary gland form pituitary stem cell.



3. Result

We enclosed a rat pituitary adenoma in a gel capsule, and hormone secretion was provided after transplant subcutaneously. We could maintain mouse marrow cell without differentiation by culturing no serum medium under zero gravity. In future, We will aim at separation and culturing of the pituitary stem cell in the human.

4. For Application

If we isolate pituitary stem cell in a zero gravity state effectively and high-density culture is enabled, pituitary stem cell can develop to pituitary cell producing a necessary hormone. We enclose these cells in a gel capsule, and become able to make artificial pituitary gland.

Competitive Advantages

The study of the pituitary stem cell is often conducted using a rat, and the study on human dose not advance. Therefore we isolate very few pituitary stem sells from a neoplastic cell provided through the operation of pituitary adenoma, and aim for multiplying it effectively.

Patent/Journal/Award

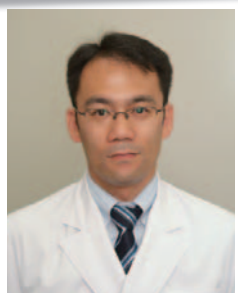
J Neurosurg 110: 369–73, 2009. Neurosurgery 63: E370–2, 2008.

URL

Life Science

The Effects on Gene Expression Profiles in Human Hepatocytes by HBV and HCV Infection

Keywords Hepatitis Virus, Human Hepatocyte Chimeric Mouse, Microarray



Masataka TSUGE
Department Natural Science Center for Basic Research and Development
Title Assistant Professor
E-mail tsuge@hiroshima-u.ac.jp
Field Gastroenterology, Hepatology

Outline

1. Background

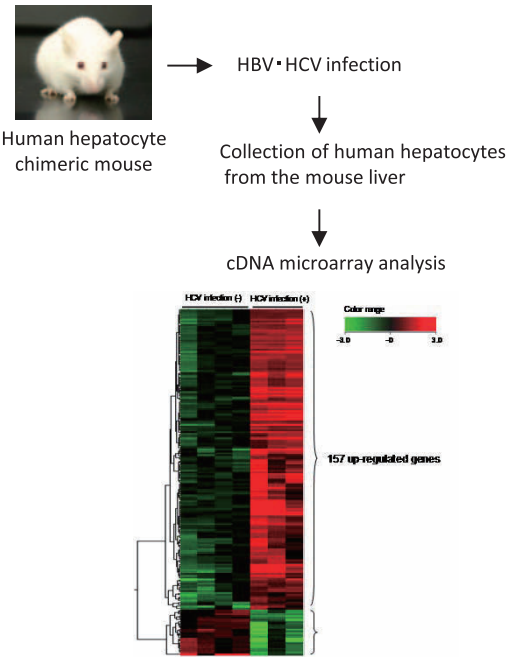
Recently, there are many reports how hepatitis B and C viruses (HBV and HCV) infection affects the gene expression in the human liver with cDNA microarray analysis, however, these analyses cannot exclude the influences of the immunological responses.

2. Research Summary

In this study, we applied human hepatocyte chimeric mice, in which T cell and B cell were depleted, and analyzed newly induced gene expression by HBV and HCV infection under immunodeficient condition.

3. Result

HBV infection affected expression of genes related to cell growth and DNA damage and repair. HCV infection affected expression of genes related to the immune system. IFN responses were significantly suppressed in IFN signaling by both HBV and HCV infection. However, some signal pathways differed, e.g., HBV infection suppressed genes related to viral recognition, and HCV infection suppressed genes related to antigen presentation.



Tsuge M, *et al*. *PLoS ONE* 2011;6:e23856.

HBV and HCV employ different molecular mechanisms to evade innate immune responses and suppress the effects of interferon therapy.

4. For Application

- Analysis of molecular mechanisms for chronic HBV and HCV infection
- Eradication of hepatitis viruses by restoring the intrahepatic immune responses
- Screening of anti-viral effects by using novel small compounds

Competitive Advantages

Human hepatocyte chimeric mice, in which liver cells were largely (>90%) replaced with human hepatocytes, were used to reduce potential influence by mouse-derived mRNA. We expect that this models will prove to be valuable applications in finding a suitable therapy against several kinds of multi-drug resistant hepatitis viruses.

Patent/Journal/Award

Journal: ① Tsuge M, Hiraga N, Takaishi H, et al. Hepatology 2005; 42: 1046–54.
② Tsuge M, Hiraga N, Akiyama R, et al. J Gen Virol 2010; 91: 1854–64.
③ Tsuge M, Fujimoto Y, Hiraga N, et al. PLoS One 2011; 6: e23856.
④ Tsuge M, Takahashi S, Hiraga N, et al. J Infect Dis 2011; 204: 224–8.
Award: GlaxoSmithKline Award (Award from the Japan Society of Hepatology, 2006), Taisho-Toyama Award (2007)

URL

Life Science

Estimation of Arterial Wall Impedance Using Ultra-sonographic Images and its Application to the Diagnosis of Arteriosclerosis

Keywords Mechanical Impedance, Arteriosclerosis, Ultrasonography

Toshio TSUJI
Department Graduate School of Engineering Title Professor
E-mail tsuji@bsys.hiroshima-u.ac.jp

Masashi KAWAMOTO
Department Institute of Biomedical & Health Sciences Title Professor
E-mail anekawa@hiroshima-u.ac.jp

Masao YOSHIZUMI
Department Institute of Biomedical & Health Sciences Title Professor
E-mail yoshizum-tky@umin.ac.jp

Field Human Medical Eng., Basic Med., Electrical/Electronic Eng.

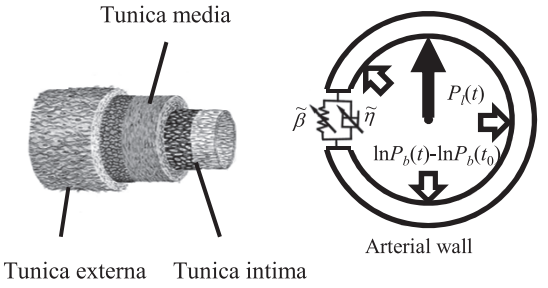
Outline

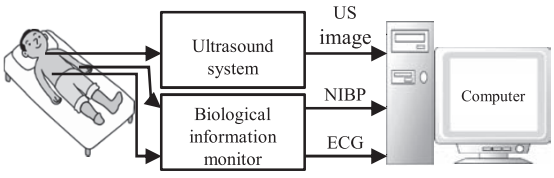
1. Background

Non-invasive determination of arterial wall characteristics is important in the early detection of arteriosclerosis, which is a progressive illness. However, the indices previously proposed to support diagnosis do not adequately consider the details of arterial wall mechanical characteristics such as viscosity, inertia and stiffness.

2. Research Summary

We propose a log-linearized arterial viscoelastic model that offers the advantage of enabling the estimation of intravascular pressure-independent arterial viscoelastic indices. The model can take non-linearity between the arterial diameter and intravascular pressure into consideration, and can be used to estimate viscoelastic indices on a beat-to-beat basis using the linear least squares method. In this study, we also estimated carotid arterial viscoelastic indices using continuous blood pressure values and carotid artery ultrasonography.





3. Result

Carotid arterial viscoelastic indices can be estimated using the model. The proposed indices exhibited the capacity to allow discrimination between healthy subjects and atherosclerotic patients.

4. For Application

A novel support system for the diagnosis of arteriosclerosis can be developed by utilizing the proposed method with arterial blood pressure-measuring apparatus and an ultrasonic device.

Competitive Advantages

The proposed model supports the estimation of arterial wall mechanical characteristics with a higher degree of accuracy than previous models. Accordingly, it has the potential to support quantitative evaluation and early detection of arteriosclerosis.

Patent/Journal/Award

T.Horiuchi, A. Kutluk, T. Tsuji, T. Ukawa, R. Nakamura, N. Saeki, Y. Higashi, M. Kawamoto, M. Yoshizumi, “A Log-learrized Arterial Viscoelastic Index and Its Application to Carotid Ultrasonography”, Proc. of 6th Western Japan Workshop on Vascular Function, p. 10, 2010.

URL
http://www.bsys.hiroshima-u.ac.jp/
http://home.hiroshima-u.ac.jp/anesth/
http://home.hiroshima-u.ac.jp/seiri1/

Life Science

Measurement of Peripheral Artery Mechanical Characteristics and Evaluation of Autonomic Nerve Activity

Keywords Mechanical Impedance, Autonomic Nerves, Arterial Wall

Toshio TSUJI
Department Graduate School of Engineering Title Professor
E-mail tsuji@bsys.hiroshima-u.ac.jp

Masashi KAWAMOTO
Department Institute of Biomedical & Health Sciences Title Professor
E-mail anekawa@hiroshima-u.ac.jp

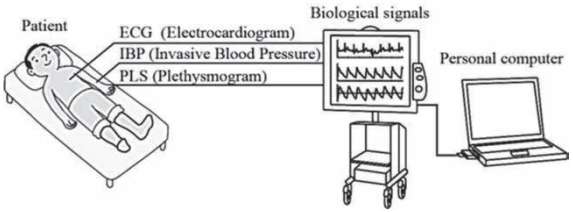
Masao YOSHIZUMI
Department Institute of Biomedical & Health Sciences Title Professor
E-mail yoshizum-tky@umin.ac.jp

Field Human Medical Eng., Basic Med., Electrical/Electronic Eng.

Outline

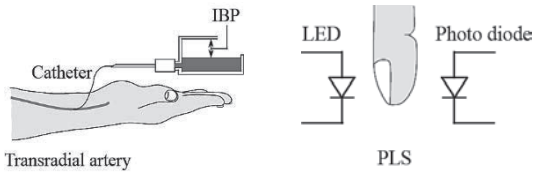
1. Background

There is significant demand for the development of a clinical or home healthcare support system that can be used to quantitatively estimate and evaluate autonomic nervous activity.



2. Research Summary

We propose a log-linearized peripheral arterial viscoelastic model that offers the advantage of enabling the estimation of intravascular pressure-independent arterial viscoelastic indices. The model can take non-linearity between the arterial diameter and intravascular pressure into consideration, and can be used to estimate viscoelastic indices on a beat-to-beat basis using the linear least squares method. In this study, it was applied to the estimation of autonomic nervous activity using continuous blood pressure values and peripheral photoplethysmograms during endoscopic thoracic sympathectomy (ETS).



3. Result

The experimental results confirmed that the model can be used to appropriately estimate acute variations of sympathetic nerve activity during ETS.

4. For Application

Using the proposed method, it is possible to develop a measurement system that can be used to quantitatively evaluate pain based on the relationship between pain and sympathetic nerve activity.

Competitive Advantages

Estimation of arterial stiffness using the proposed model enabled superior objective evaluation of sympathetic nerve activity caused by events during ETS.

Patent/Journal/Award

Japanese Patent No. 4590630, BLOOD VESSEL WALL MONITORING APPARATUS, CONTROL PROGRAM AND RECORDING MEDIUM WITH PROGRAM READABLE BY COMPUTER STORED THEREIN

H. Hirano, H. Tetsuya, H. Maruyama, H. Hirano, A. Kutluk, T. Tsuji, T. Ukawa, R. Nakamura, N. Saeki, M. Yoshizumi, M. Kawamoto, Log-linearized Peripheral Arterial Viscoelastic Indices Using a Photoplethysmogram, Proc. of the 2011 JSME Conf. on Robotics and Mechatronics, 2P1-B06 (1–4), 2011.

URL http://www.bsys.hiroshima-u.ac.jp/ http://home.hiroshima-u.ac.jp/anesth/ http://home.hiroshima-u.ac.jp/seiri1/

Life Science

Non-constrained and Non-invasive Measurement of Pulse Pressure Waves from Patients in a Supine Position and Development of a Health Monitoring System for Bedridden Individuals

Keywords Health Monitoring, Pulse Pressure Waves, Non-Binging

Toshio TSUJI
Department Graduate School of Engineering Title Professor
E-mail tsuji@bsys.hiroshima-u.ac.jp

Masashi KAWAMOTO
Department Institute of Biomedical & Health Sciences Title Professor
E-mail anekawa@hiroshima-u.ac.jp

Masao YOSHIZUMI
Department Institute of Biomedical & Health Sciences Title Professor
E-mail yoshizum-tky@umin.ac.jp

Field Human Medical Eng., Basic Med., Electrical/Electronic Eng.

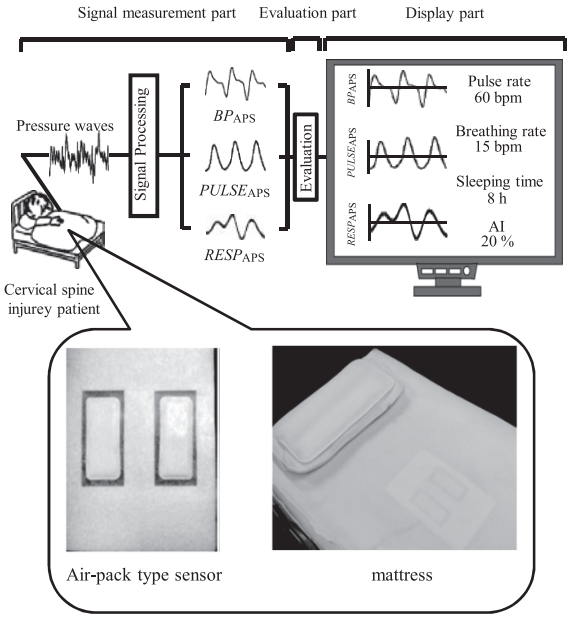
Outline

1. Background

Most patients with cervical spinal cord injuries receive treatment at home, and those suffering from related quadriplegia need life support and round-the-clock monitoring from a care worker, a healthcare professional or a family member. However, as it is difficult for such observers to constantly monitor the patient's condition, a system that can perform this task in place of an observer is required.

2. Research Summary

A 24-hour monitoring system must fulfill the following requirements: (1) it must detect urgent dangers such as arrhythmia and the cessation of breathing and alert a healthcare professional; (2) it must detect chronic dangers to the circulatory system such as abnormal blood pressure and arteriosclerosis; (3) it must have prophylactic functions to prevent decubitus ulcers in quadriplegic patients; (4) it must be able to monitor the patient's biological signals in a non-constrained manner over a long period; and (5) it must be easy to use.



3. Result

We developed a monitoring system that can be used to prevent decubitus and measure pulse pressure waves/ breathing waves via a pair of air-pack-type pressure sensors in a non-constrained and non-invasive manner.

4. For Application

The capacity to monitor patients over long periods is expected to reduce the burden on caregivers.

Competitive Advantages

This system can be used to measure pulse pressure waves and breathing waves in a non-constrained and non-invasive way. A distinctive feature of the system is that it can calculate the cardiac rate and the augmentation index simultaneously and automatically. It is useful in the diagnosis and monitoring of bedridden patients.

Patent/Journal/Award

Japanese Patent Application No. 2009–118095 abdominal aortic aneurysm detecting device

URL http://www.bsys.hiroshima-u.ac.jp/ http://home.hiroshima-u.ac.jp/anesth/ http://home.hiroshima-u.ac.jp/seiri1/

Life Science

Understanding the Mechanism of Chromosome End Maintenance and its Application for Cancer Therapy

Keywords Anticancer Drug, DNA Repair, Chromosome Segregation, Telomere, Genome

Masaru UENO

Department Graduate School of Advanced Sciences of Matter

Title Associate Professor

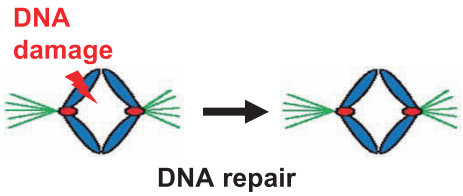
E-mail scmueno@hiroshima-u.ac.jp

Field Basic Biology, Chromosome Dynamics

Outline

1. Background

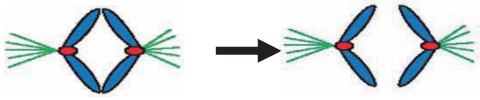
Inhibitors of DNA repair and chromosome segregation are used as anticancer drugs. As the maintenance of chromosome ends called telomeres is essential for immortality of cancer cells, telomere maintenance could be a target for anticancer drugs.



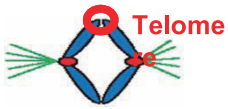
DNA repair

2. Research Summary

We use fission yeast to study DNA repair, chromosome segregation and telomere maintenance. During these researchs, we created many interesting fission yeast mutants that could be used for the screening of chemical compounds that inhibit DNA repair, chromosome segregation or telomere maintenance.



Chromosome segregation



Telomere maintenance

3. Result

We have revealed new functions of several proteins involved in DNA repair, chromosome segregation and telomere maintenance in fission yeast.

4. For Application

Several fission yeast mutants that we created could be used for the screening of chemical compounds that inhibit DNA repair, chromosome segregation or telomere maintenance.

Competitive Advantages

We have published many high level papers about DNA repair and telomere maintenance in fission yeast. We have special knowledge and many unique mutants related to DNA repair, chromosome segregation and telomere maintenance in fission yeast that can be applied for the screening of new anticancer drugs.

Patent/Journal/Award

Mol. Cell. Biol. **31**, 495–506. (2011) - Japan Society for Bioscience, Biotechnology, and Agrochemistry Award for the Encouragement of Young Scientists -

URL http://home.hiroshima-u.ac.jp/scmueno/index.html

Life Science

Effect of the Water-soluble Extract from Cultured Medium of Ganoderma Lucidum (Reishi) Mycelia (MAK) on Murine Colitis

Keywords MAK, Colitis, GM-CSF

Yoshitaka UENO

Department Hiroshima University Hospital
Title Assistant Professor

E-mail yueno@hiroshima-u.ac.jp
Field Gastroenterology

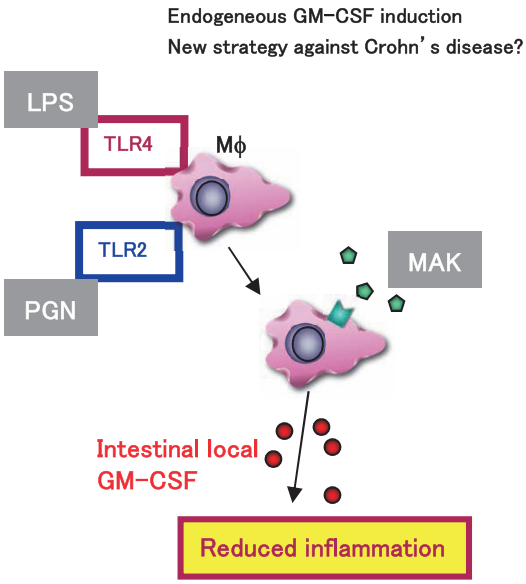
Outline

1. Background

Ganoderma lucidum Karst is well known as “Rei-shi”, a traditional food in China and Japan. It contains various immunomodulating substances, including polysaccharides, terpenoids, and cerebrosides. However, so far, there have been no reports demonstrating the effect of MAK on intestinal inflammation.

2. Research Summary

The effect of MAK on murine colitis induced by trinitrobenzene sulphonic acid (TNBS) is investigated. The concentration of GM-CSF in peritoneal macrophage cells (PMs) of C57BL/6 mice is examined during *in vitro* stimulation with MAK. After feeding with MAK, TNBS is administered to each mouse. After 3 days of TNBS-treatment, intestinal inflammation is evaluated, and colon is cultured for ELISA. To determine the preventive role of GM-CSF, the mice are pretreated with or without anti GM-CSF antibody before TNBS administration.



3. Result

In vitro MAK-stimulated PMs produced GM-CSF in a dose-dependent manner. Intestinal inflammation by TNBS was improved by feeding with MAK. The colon organ culture assay also revealed that GM-CSF was increased by MAK. The preventive effect was blocked by the neutralization of GM-CSF.

4. For Application

MAK is commercially available in Japan and its safety is warranted.

Competitive Advantages

Systemic administration of GM-CSF is effective in the treatment of patients with CD. However, several adverse effects, such as injection site reaction or bone pain are often seen. Our concept that induction of endogenous GM-CSF is a target for the treatment of inflammatory bowel disease may reduce such adverse effects.

Patent/Journal/Award

Scand J Immunol 2011; 74: 454–462

URL http://home.hiroshima-u.ac.jp/mml/

Life Science

Mechanism, Prediction and Countermeasure of Problematic Jellyfish Blooms

Keywords Common Jellyfish, Giant Jellyfish, Monitoring, Marine Coastal Management

Shin-ichi UYE

Department Graduate School of Biosphere Science

Title Professor (Executive, Vice-President)

E-mail suye@hiroshima-u.ac.jp

Field Environmental Science, Fisheries Science, Basic Biology

Outline

1. Background and Objective

Frequent occurrence of the common jellyfish (*Aurelia* spp.) and the giant jellyfish (*Nemopilema nomurai*) blooms in East Asian seas cause serious problems in fisheries and power station operation. It is urgent to diminish the damage by such jellyfish outbreaks.

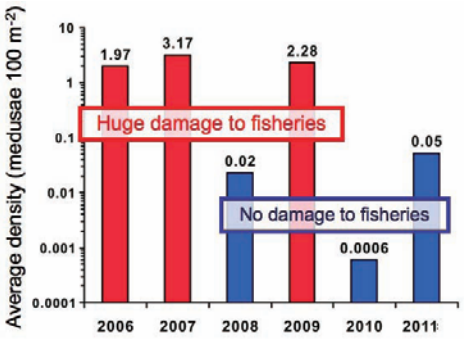
Massive giant jellyfish gave serious damage to set-nets along the Japnese coast, causing monetary loss of ca. 30 billion JPY in 2005.

2. Research Summary

Studies are in progress to clarify causes for the jellyfish blooms and to predict the intensity of jellyfish bloom in advance. Studies are also undertaken to develop environment-friendly techniques to kill jellyfish polyps.

3. Results

Major causes for the jellyfish blooms are 1) overfishing, 2) global warming, 3) eutrophication, and 4) marine construction, all derived from human activity. It is of prime importance to preserve healthy ecosystem with high biodiversity in order to prevent frequent jellyfish outbreaks. Our monitoring program of Nemopilema young medusae in the Yellow and East China Seas enables us to predict the giant jellyfish bloom in 1–3 months in advance.



Year-to-year variation in mean density of *Nemopilema* young medusae in the Yellow Sea. Based on these monitoring results, we can predict the jellyfish bloom intensity.

4. For Application

Jellyfish bloom prediction based on our monitoring is useful for fishermen and coastal power stations in order to tackle in advance possible jellyfish attack.

Competitive Advantages

Our studies aiming at prediction of jellyfish bloom intensity and control of jellyfish polyp population are novel, and our models and techniques are applicable to other problematic jellyfish blooms outside Japan.

Patent/Journal/Award

Award: The Oceanographical Society of Japan Prize (2010 年)

URL http://home.hiroshima-u.ac.jp/hubol/members/uye.html

Life Science

Mechanism of Chronic Pain in Orofacial Region

Keywords Allodynia/Hyperalgesia, Mental Nerve, Nerve Injury, IL-1β

Mineo WATANABE

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail mineo@hiroshima-u.ac.jp

Field Dental

Outline

1. Background

In orofacial region, chronic pain frequently happen, although very little knowledge has been acquired. In addition, it is very difficult to treat chronic pain.

2. Research Summary

We examined the mechanism of neuropathic pain in orofacial region and tried to find a therapeutic method. We used rats. Mental nerve was transected. Then, allodynia/hyperalgesia on whisker pad area was evaluated. We also examined expression of IL-1beta and effect of IL-1beta antagonist on allodynia/hyperalgesia.

3. Result

After mental nerve transection, hyperalgesia developed on the ipsilateral whisker pad area. IL-1beta was up-regulated in the brain. Allodynia/hyperalgesia at WP area induced by MN transection was attenuated dose-dependently by IL-1 receptor antagonist.

4. For Application

Drug maker/Basic science of chronic pain.

We can do animal experiment for chronic pain. However, it is very difficult to do clinical research.

We need investigational drug for chronic pain from a drug maker.

Competitive Advantages

There are very few lab. that can evaluate chronic pain in orofacial region using animal in the world.

Patent/Journal/Award

Takahashi K, Watanabe M, Suekawa Y, Ito G, Inubushi T, Hirose N, Murasaki K, Hiyama S, Uchida T, Tanne K. IL-1beta in the trigeminal subnucleus caudalis contributes to extra-territorial allodynia/hyperalgesia following a trigeminal nerve injury. Eur J Pain. 2011 May; 15 (5): 467. e1–14.

URL http://www.ncbi.nlm.nih.gov/pubmed?term=.%20IL-1beta%20in%20the%20trigeminal%20subnucleus%20caudalis%20contributes%20to%20extra-territorial%20allodynia%2Fhyperalgesia%20following%20a%20trigeminal%20nerve%20injury.%20

Life Science

Algal Synthesis of Hyaluronan and Chitin

Keywords Chlorella, Hyaluronan (HA), Chitin (CH), Chlorella Virus (Chlorovirus)

Takashi YAMADA

Department Graduate School of Advanced Sciences of Matter

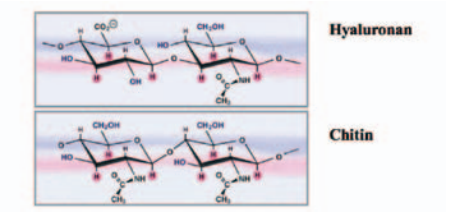
Title Professor

E-mail tayamad@hiroshima-u.ac.jp Field Applied Microbiology, Process Engineering, Agricultural Chemistry

Outline

1. Background

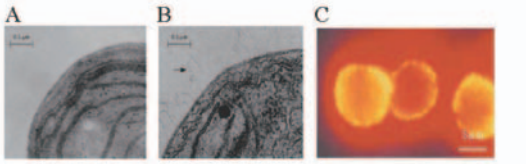
Reflecting their wide variety of biological functions, the applications of hyaluronan (HA) as well as chitin (CH) and chitooligosaccharides extend into various fields such as medicine (including surgery), cosmetics, health food, etc. To meet ever-increasing public demand, novel systems that can afford sufficient amounts of high-quality materials are required. We have developed a novel system to produce both HA and chitin by chlorella cells using Chlorovirus.



Reflecting the wide variety of biological functions, both hyaluronan and chitin have extended the applications in various fields including medicine, surgery, cosmetics, health-care, food etc.

2. Research Summary

Chloroviruses or *Chlorella* viruses are large icosahedral, plaque-forming, double-stranded DNA- containing viruses that infect certain strains of the unicellular green algae *Chlorella*. Chlorovirus contains a gene that encodes a function for hyaluronan or chitin synthesis (some chloroviruses contain both genes), which is expressed early in viral infection to produce hyaluronan (HA) or chitin (CH) on the outside of *Chlorella* cell wall. The synthesis of HA or CH in this system was analyzed.



Hyaluronan (HA) accumulation on the virus-infected *Chlorella* cells.HA fibers cover the cell surface shortly after virus infection(B, C).

3. Result

Experimentally, approximately 0.1–0.5 g hyaluronan was recovered from a 1L culture of Chlorella cells infected with Chlorovirus (for 3h). Synthesized HA chains composed of ac 10^4 sugars (3–6 x 10^6 Da). In some cases, CH was produced in a similar way.

4. For Application

Medicine (including surgery), cosmetics, health food, etc.

Competitive Advantages

This system can be integrated with biomass utilization, light-energy conversion and CO_2-fixation. Unlike fermentation systems with *Streptococccus* spp., there is no risk of contamination with toxic compounds. No chemical treatment (acid/alkali/organic solvent) is involved.

Patent/Journal/Award

Japanese Patent Nos. 3989865 and 3989866,
J. Biosci. Bioeng., 99: 521–528 (2005), Virology, 302:123–131 (2002), Adv, Virus. Res. 66: 293–336 (2006),
Bioengineering Excellent Achievement Award (2009)

URL http://home.hiroshima-u.ac.jp/mbiotech/ichikou/itikouindex.html

Life Science

Bacteriophage Biocontrol of Bacterial Wilt for Sustainable Agricultural Production

Keywords Bacterial Wilt, *Ralstonia Solanacearum*, Bacteriophage, RSM, RSL

Takashi YAMADA

Department Graduate School of Advanced Sciences of Matter

Title Professor

E-mail tayamad@hiroshima-u.ac.jp

Field Applied Microbiology, Process Engineering, Agricultural Chemistry

Outline

1. Background

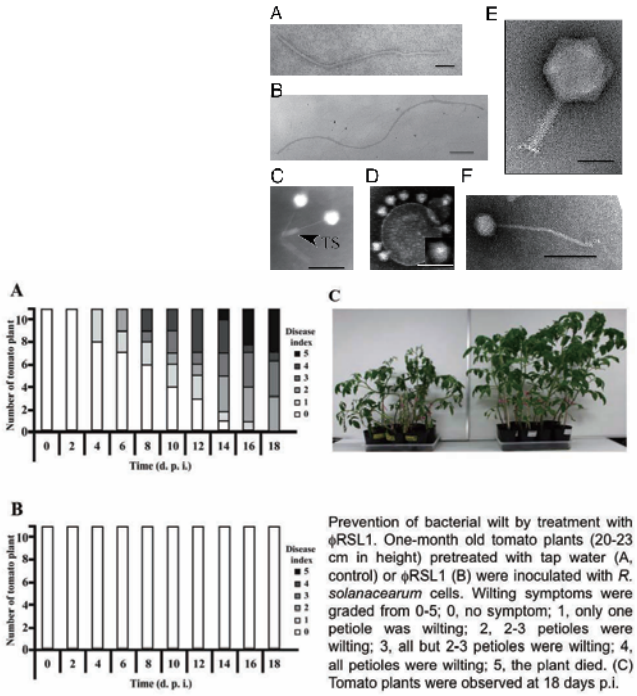
Bacterial wilt caused by *Ralstonia solanacearum* is an important plant disease of many crops, damaging more than 200 species in 50 botanical families, occurring widely in the world, and persisting in the environment. Various measures have been tried to control this disease without stable effectiveness. Thus alternative control methods for bacterial wilt, which are more effective, safer to applicators and with lower environmental impact, are still needed.

2. Research Summary

Instead of harmful chemicals, we are interested in utilization of natural enemies of the bacteria, bacteriophages. Among many phages which we isolated and highly characterized, two were found to be useful for biocontrol purposes. RSL1, a jumbo phage of Myoviridae stably inhibits growth of the bacteria. RSM, filamentous phage of Inoviridae converts the host cells to avirulent.

3. Result

All ϕRSL1-treated tomato plants showed no symptoms of wilting during the experimental period, whereas all untreated plants had wilted in 18 days post-infection. This protection lasted at least 2 months. ϕRSM3-infected cells enhanced the expression of pathogenesis related genes in tomato plants. Moreover, pre-treatment with ϕRSM-infected cells protect tomato plants from infection by virulent *R. solanacearum* strains. This vaccine effects worked for two months.



Prevention of bacterial wilt by treatment with ϕRSL1. One-month old tomato plants (20-23 cm in height) pretreated with tap water (A, control) or ϕRSL1 (B) were inoculated with *R. solanacearum* cells. Wilting symptoms were graded from 0-5; 0, no symptom; 1, only one petiole was wilting; 2, 2-3 petioles were wilting; 3, all but 2-3 petioles were wilting; 4, all petioles were wilting; 5, the plant died. (C) Tomato plants were observed at 18 days p.i.

ASM

4. For Application

These methods with phages RSL and RSM are recommended to apply to plant seedlings before planting in the fields. Because all bacterial strains tested are susceptible to RSM1 or RSM3, these phages are useful to convert field isolated pathogens to avirulent for prevention of wilt spread.

Competitive Advantages

(i) Harmless to natural ecosystems, (ii) very effective because phages propagate exponentially with host cells, (iii) not expensive and easy mass cultivation, (iv) easy handling.
In combination with appropriate detection and diagnosis methods, this prevention and control will be most effective.

Patent/Journal/Award

Japanese Patent No.4532959, Patenat Application No.JP 2011–102153;
Appl. Environ. Microbiol.,77:4155–4162(2011), Phytopathology,102(5) (2012) in press, Plant Dis.,96(6)(2012) in press.
Bioengineering Excellent Achievement Award (2009)

URL http://home.hiroshima-u.ac.jp/mbiotech/ichikou/itikouindex.html
http://www.intechopen.com/books/bacteriophages/bacteriophages-of-ralstonia-solanacearum-their-diversity-and-utilization-as-biocontrol-agents-in-agr

Life Science

Detection and Monitoring of Phytopathogen Causing Bacterial Wilt

Keywords Bacterial Wilt, *Ralstonia Solanacearum*, Bacteriophage, RSM, RSS

Takashi YAMADA

Department Graduate School of Advanced Sciences of Matter

Title Professor

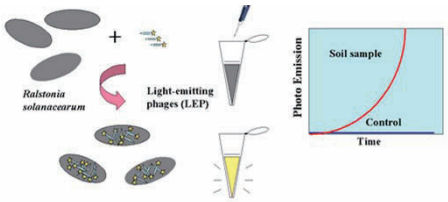
E-mail tayamad@hiroshima-u.ac.jp

Field Applied Microbiology, Process Engineering, Agricultural Chemistry

Outline

1. Background

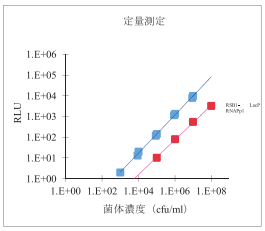
Bacterial wilt caused by *Ralstonia solanacearum* is an important plant disease of many crops since it damages more than 200 species in 50 botanical families, occurs widely in the world, and persists in the environment. A variety of methods have been developed to detect the pathogen but none of them can reliably detect it either in plants and soils, or in soil-related habitats. We propose utilization of filamentous bacteriophages as reporters to quantify and monitor bacterial cell number in the natural environment.

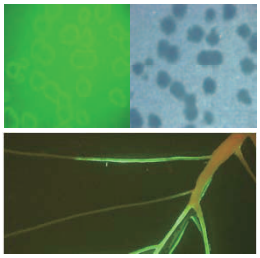


Detection of *R. solanacearum* cells using LEP (method 2).

2. Research Summary

RSM and RSS are filamentous phages of Inoviridae infecting specifically strains of *R. solanacearum*.. They were genetically modified to express reporter genes such as GFP or luciferase in infected host cells. Bacterial cells with GFP or luciferase signal could be easily detected at high sensityvity. Plasmid derived from these phage genomes were also demonstrated to be useful as cloning vectors for *R. solanacearum*. Labeled bacterial cells can be easily monitored in plant cells and natural environments.





3. Result

GFP- or luciferase-expressing RSS phages (plasmids) detected 10^2 cells/g sample of *R. solanacearum*. Growth and movement of GFP-labeled cells could be easily monitored in tomato plants as well as in field soils. All strains tested of different races and/or biovars could be detected by RSM phages.

4. For Application

GFP- or luciferase-expressing RSS phages (plasmids) can be used as a detection tool for *R. solanacearum* cells in the environments. They may also work for diagnosis for bacterial wilt. This detection method will be more effective in combination with appropriate prevention and control technologies. The detection and monitoring method is also useful in breeding plant culivars resistant to bacterial wilt.

Competitive Advantages

Compared with other methods such as PCR and ELISA, phage method can detect only viable and active cells in the environments, giving reliable data. Environmental noise and disturbing factors can be reduced.

Patent/Journal/Award

Japanese Patent No. 4532959, Patent Application Nos. JP 2007–228396 and 2009–192635
J. Biosci. Bioeng., 104: 451–456 (2007), J. Biosci. Bioeng.,109: 153–158 (2010).
Bioengineering Excellent Achievement Award (2009)

URL

http://home.hiroshima-u.ac.jp/mbiotech/ichikou/itikouindex.html
http://www.intechopen.com/books/bacteriophages/bacteriophages-of-ralstonia-solanacearum-their-diversity-and-utilization-as-biocontrol-agents-in-agr

Life Science

How Does Habitat Association of Plant Species Generate and Maintain?

Keywords Plant Ecology, Tropical Ecology, Forest Ecology

Toshihiro YAMADA
Department Graduate School of Integrated Arts and Sciences
Title Associate Professor
E-mail yamada07@hiroshima-u.ac.jp Field Biology

Outline

1. Background

Tropical forests are rapidly decreasing their area. Then ecosystem services by tropical forests are thus being lessened.

2. Research Summary

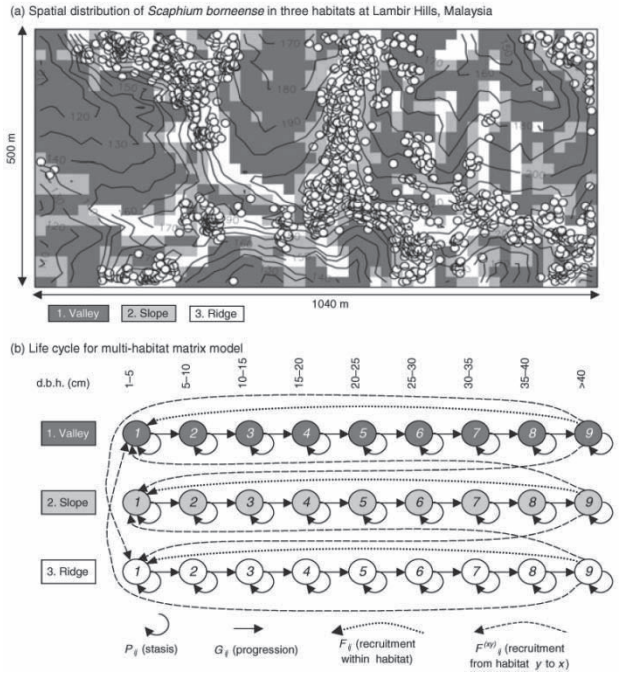
How can we stop and/or delay decrease in tropical forest areas?
What is the effective mechanism to do it?
I am seeking the answers of the questions.

3. Result

I found that exchange of seed between habitats plays a key role in the maintenance of biodiversity in tropical forests.
As a mechanism for conservation of tropical forests, I am doing researches on implementation of redd for Southeast Asian tropical forest managements.

4. For Application

I would like to make our idea be taken in Japanese policy.



Competitive Advantages

Patent/Journal/Award

① Yamada, T. S. Aiba, Y. Kubota, K. Okubo, I. Miyata, E. Suzuki, H. Maenaka, M. Nagano. Dynamics of species diversity in a Japanese warm-temperate secondary forest. Ecosphere 2: art80. 2011
② Zuidema, P., Yamada, T., Itoh, A., Yamakura, T., Ohkubo, T., Kanzaki, M., Tan, S., Ashton, P.S., Recruitment subsidies support tree subpopulations in non-preferred tropical forest habitats, Journal of Ecology, 98, 636–644. 2010

URL

Life Science

Neural Regeneration by Application of Human Skull Mesenchymal Stem Cells

Keywords Human Bone Marrow Stem Cell, Regenerative Neuroscience

Satoshi YAMAGUCHI
Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail satoya@hiroshima-u.ac.jp
Field Neurology, Neurosurgery

Outline

1. Background

Regenerative medicine with pluripotent stem cell has notably progressed. The application of this novel technology to neural intractable diseases has just begun.

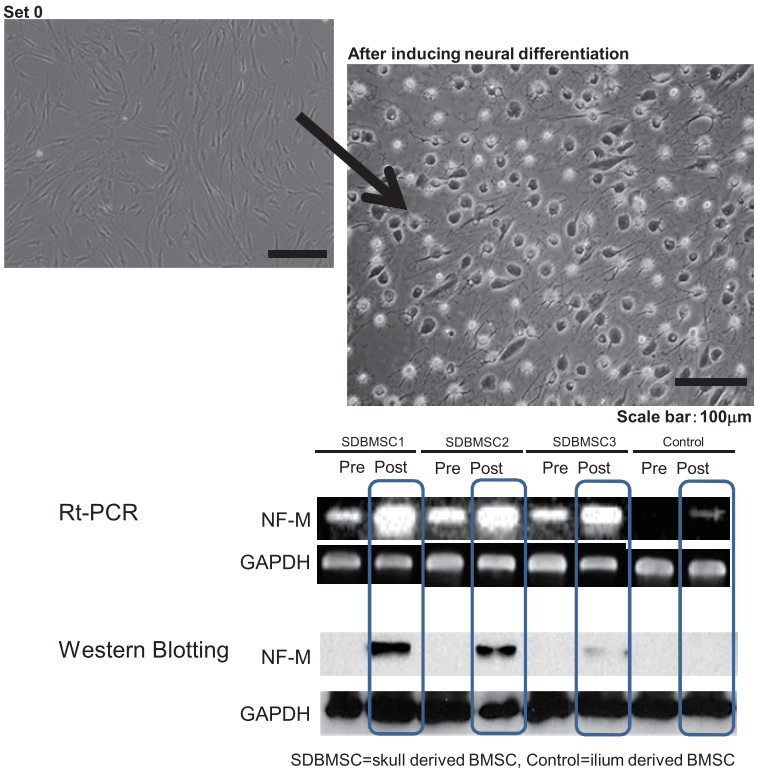
2. Research Summary

Although bones in the extremities are derived from mesoderm, the skull is derived from neuroectoderm. Human bone marrow stem (hBMSC) cell extracted from the skull may have the potential to differentiate into the neural tissue. We are trying to culture hBMSC and to induce neural differentiation.

3. Result

After neural induction of hBMSC, hBMSC showed morphological change into bi- or multi-polar neuron-like cell. Rt-PCR and western blotting confirmed neural markers, NF-M.

Morphological features of human skull mesenchymal stem cells



SDBMSC=skull derived BMSC, Control=ilium derived BMSC

4. For Application

Regenerative medicine using hBMSC may be applied to intractable neural diseases.

Competitive Advantages

Regenerative technology using hBMSC has high originality compared with other BMSC-based studies.

Patent/Journal/Award

URL

Life Science

Development of Engineered Nucleases that Enable the Manipulation of the Genome in Cell Lines and Organisms

Keywords Genome Editing, Engineered Nucleases, Mammalian Cells

Takashi YAMAMOTO

Department Graduate School of Science

Title Professor

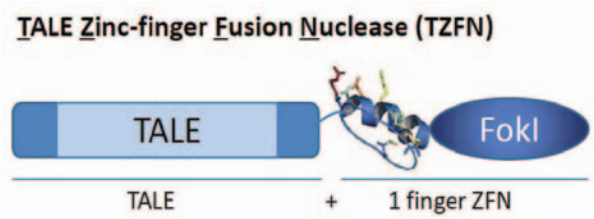
E-mail tybig@hiroshima-u.ac.jp

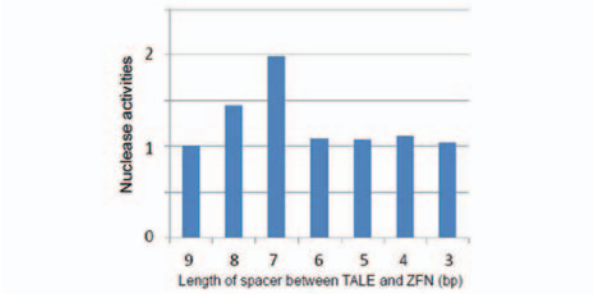
Field Genome Biology

Outline

1. Background

However, this approach is only available in limited models, such as the mouse. Recently, a new method for genetic modification called genome editing, using engineered nucleases, such as zinc finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), has been reported in several organisms and mammalian cells.





2. Research Summary

ZFN and TALEN technologies provide strong tools for genomic manipulation, yet their setup and efficiency require significant improvement to be useful to all researchers. To make the ZFN/TALEN technologies readily available and to optimize their efficiency for all researchers, we generated TALE-zinc finger fusion nucleases (TZFNs) and evaluated their activity in mammalian cells. It is postulated that the TALE at the N-terminus of TZFN allows researchers to design target sequences as required and that the ZFN at the C-terminus of TZFN specifies a better digestion site for the Fok1 enzyme.

3. Result

A single strand annealing assay (SSA) for measuring nuclease activity showed that a TZFN with a 7bp spacer between the TALE and the zinc-finger had relatively high nuclease activity. To develop this TZFN with high nuclease activity, we will need to revise its N-/C-termini.

4. For Application

TZFN are useful for genome editing in mammalian cells. This result contributes to the goal of producing cells harboring genetic disease mutations.

Competitive Advantages

TZFN enables the scientists to manipulate the genome more efficiently and precisely.

Patent/Journal/Award

・Ochiai H, Fujita K, Suzuki K, Nishikawa M, Shibata T, Sakamoto N and Yamamoto T. Targeted mutagenesis in the sea urchin embryo using zinc-finger nucleases. *Genes Cells*, **15**: 875–885, 2010

URL

Life Science

Development of Automatic Diagnostic System for Brain Tumors

Keywords Brain Tumor, Diagnostic System

Fumiyuki YAMASAKI
Department Institute of Biomedical & Health Sciences
Title Assistant Professor
E-mail fyama@hiroshima-u.ac.jp
Field Neurosurgery

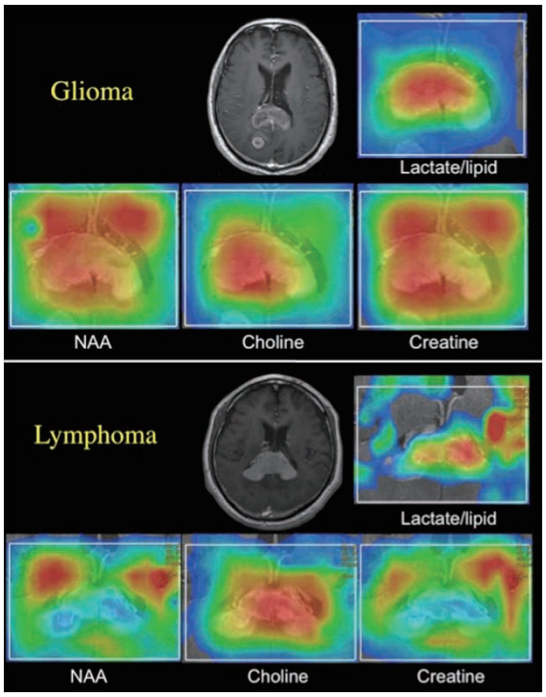
Outline

1. Background

Preoperative differential diagnosis is very important because the therapeutic strategy is different depending on the type of brain tumor. However, differential diagnosis by conventional MR imaging is sometimes very difficult. We conducted the clinical study of differential diagnosis to develop automatic diagnosis system based on advanced MR imaging.

2. Research Summary

We evaluated diffusion-weighted imaging including high b value based diffusion weighted imaging for differential diagnosis. We also evaluated validity of MR spectroscopy, perfusion-weighted imaging and magnetic susceptibility-weighted imaging for differential diagnosis.



3. Result

We verified the advantage of high b value based diffusion-weighted imaging for differential diagnosis. We also confirmed the advantage of detecting lactate and lipids with MR spectroscopy by varying echo time.

4. For Application

We currently overlay the advanced MR images manually. Automatic system for combination of images is required for practical application.

Competitive Advantages

Advanced MR imaging is superior to conventional system because of availability of quantitative data of each parameter.

Patent/Journal/Award

Eur J Radiol. 81:339–344, 2012.
Eur J Radiol. 80:412–417, 2011.
Eur J Radiol. 73:532–537, 2010.
Eur J Radiol. 74:420–7, 2010.
Radiology. 235:985–991, 2005.
Neurosurg Rev. 28:267–277, 2005.

URL http://seeds.hiroshima-u.ac.jp/soran/e33a55g/r.html

Life Science

Regulation of Thyroid Hormone Sensitivity by Differential Expression of the Thyroid Hormone Receptor During *Xenopus* Metamorphosis

Keywords Amphibia, Metamorphosis, Thyroid Hormone, Thyroid Hormone Receptor, Apoptosis

Yoshio YAOITA

Department Graduate School of Science

Title Professor

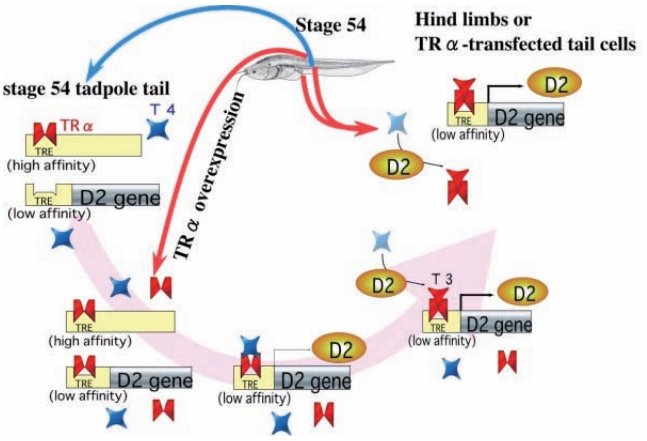
E-mail yaoita@hiroshima-u.ac.jp

Field Developmental Biology, Molecular Biology

Outline

1. Background

During amphibian metamorphosis, a series of dynamic changes occur in a predetermined order, as levels of thyroid hormone (TH) increase. Hind limb morphogenesis begins in response to low levels of TH, but tail resorption is delayed a month later until climax, when TH levels are maximal.



2. Research Summary

To study the molecular basis of the timing of tissue-specific transformations, we introduced thyroid hormone receptor (TR) expression constructs into tail muscle cells of Xenopus tadpoles, treated them with low levels of TH, and analyzed apoptosis of TR-overexpressing cells.

3. Result

The TR-transfected tail muscle cells died upon exposure to a low level of thyroxine (T4). This cell death was mediated by type 2 iodothyronine deiodinase (D2), which converts T4 to T3—the more active form of TH. D2 mRNA was induced in the TR-overexpressing cells by low levels of TH. D2 promoter contains a TH response element (TRE) with a lower affinity for TR. These results show that the TR transfection confers the ability to respond to low levels of TH to tail muscle cells through D2 activity, and promotes TH signaling. We propose the positive feedback loop model to amplify the cell's ability to respond to low levels of T4.

4. For Application

This study is a basic research, which explains for the first time as to why hind limb growth precedes tail resorption during amphibian metamorphosis.

Competitive Advantages

Patent/Journal/Award

Genes to Cells (in press)

URL http://home.hiroshima-u.ac.jp/%7eamphibia/YaoitaG/index.html

Life Science

Novel Diagnostic and Therapeutic Targets of Gastrointestinal Cancer Identified by "Omics" Study

Keywords Cancer-related Genes, Novel Diagnostic and Therapeutic Target, Gastrointestinal Cancer

Wataru YASUI

Department Institute of Biomedical & Health Sciences

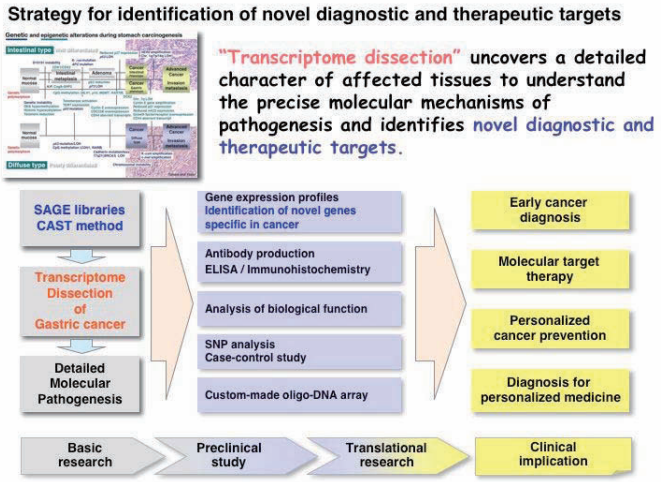
Title Professor

E-mail wyasui@hiroshima-u.ac.jp Field Human Pathology, Experimental Pathology

Outline

1. Background

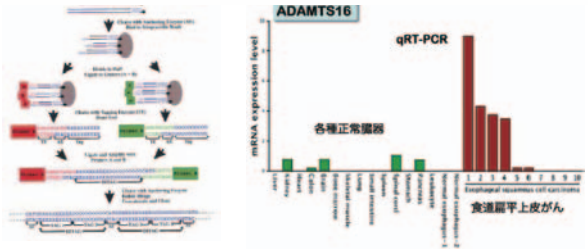
"Omics" study uncovers a detailed character of entire genome, transcriptome, proteome, RNAome, etc. in affected tissues, to identify novel diagnostic and therapeutic targets.



2. Research Summary

Transcriptome dissection of cancers of the esophagus, stomach and prostate was analyzed through Serial analysis of gene expression (SAGE) and *Escherichia coli* ampicillin trap (CAST) method. microRNA signature was analyzed in gastric cancers by microarray. Function and diagnostic and therapeutic implication were studied in novel genes and microRNAs.

3. Result



One of the largest gastric cancer SAGE libraries in the world was created (GEO accession number GSE 545). Reg IV, OLFM4, ADAMTS16, SPC18, DSC2 and TSPAN8 were identified as candidate diagnostic and therapeutic targets. Specific microRNA signatures associated with progression and prognosis of gastric cancer were identified.

4. For Application

Information obtained from the Omics studies greatly contributes to new developments for diagnosis and treatment of cancer. Development of diagnostic system and large-scale multi-center study are crucial for clinical application.

Competitive Advantages

SAGE can identify genes unanalyzable by microarray. Four institutes perform SAGE on gastric cancer in the world and only our laboratory in Japan. Analysis of gastric and prostate cancers by CAST method is conducted only at our institute in the world. By these analyses, identification of unique targets is possible.

Patent/Journal/Award

Japanese Patent Application Nos. JP 2007-015630 and 2008-005023

Cancer Res, PNAS, Lancet Oncol, Nature Med, Gastroenterology, Oncogene

Japan Pathology Award 2008

URL http://home.hiroshima-u.ac.jp/byori1/

Life Science

Clinical and Radiographical Results of 179 Thrust Plate Hip Prosthesis －5-14 Years Follow-up Study－

Keywords Bone Preserving Prosthesis, Thrust Plate Prosthesis, THA

Yuji YASUNAGA

Department Institute of Biomedical & Health Sciences

Title Professor

E-mail yasuyuji@hiroshima-u.ac.jp Field Biomedical Engineering, Biomaterial

Outline

1. Background

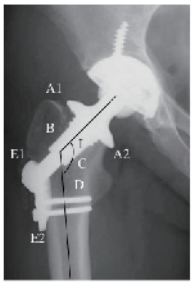
The thrust plate hip prosthesis(TPP) is a bone-reserving prosthesis for cementless fixation at the metaphysis of the proximal femur. We retrospectively evaluated the results of 162 patients (179 hips) who underwent hip arthroplasty using TPP.

2. Research Summary

Eighty-three patients (87 hips) suffered from osteoarthritis of the hip joint (OA group), 79 patients (92 hips) from osteonecrosis of the femoral head (ON group). The mean age at surgery was 55 years in the OA group and 47.4 years in the ON group. The mean follow-up period was 97 months in the OA group and 104 months in the ON group. For these patients, we evaluated the results clinically and radiographically.

3. Result

The mean Merle d'Aubigne's score improved from 8.2 to 16.9 in the OA group and from 9.1 to 16.6 in the ON group at the final follow-up. Early mechanical loosening of TPP was observed in two hips of OA and one hip of ON. In one patient of ON, bilateral TPPs had to be removed five years postoperatively because of infection. Two female patients with ON suffered from a spontaneous femoral fracture below the tip of the lateral plate. Kaplan-Meier survivorship using TPP removed for any reason as the end point was 97.7% in the OA group and 90.3% in the ON group after 13 years.



4. For Application

The TPP has been discontinued since 2006, but neither for functional defect nor lack of material quality. From a perspective of bone preservation and physiological load transmission, it was a remarkable joint prosthesis and comparable to long-term solution such as conventional implant. Therefore early restoration is desirable.

Competitive Advantages

Because of its bone-preserving model, it is a useful implant for young people who are compelled to have a hip replacement arthroplasty. In recent years, the focus is on metal-on-metal hip implant, which is a surface replacement and capable of bone-preservation. However, reports are emerging from many facilities about the side effect inducing pseudo-tumor due to be considered caused by metal wear. TPP has no such side effect, and is a very safety hip joint.

Patent/Journal/Award

Arch Orthop Trauma Surg. 2012 132:547–54.
Arch Orthop Trauma Surg. 2004 124:357–62.
J Orthop Sci. 2003;86:818–22.

URL

Life Science

Biological Psychology of Fish

Keywords Biological Psychology, Behavior, Fish, Neuroethology

Masayuki YOSHIDA

Department Graduate School of Biosphere Science
Title Associate Professor

E-mail yosidam@hiroshima-u.ac.jp
Field Animal Physiology and Behavior

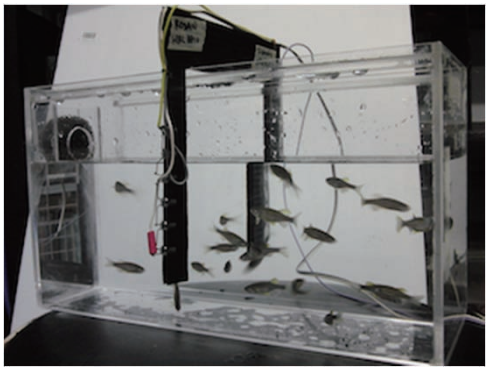
Outline

1. Background

Biological bases of species-specific psychological states underlying various behaviors are current topics.

2. Research Summary

Roles of the cerebellum in fear learning.
Understanding “fish mind” from behavioral-neuroscience point of view.



3. Result

Cerebellar structure is shared by various vertebrates and hence the “small” brain of the fish is advantageous to understand fundamental neural mechanisms underlying fear.

4. For Application

Application to aquaculture.

Competitive Advantages

Consideration of fish welfare in fisheries that should be a matter in the near future in Japan.

Patent/Journal/Award

2 awards, 3 patents pending

URL http://sites.google.com/site/biopsychologylab/Home

Life Science

Quantitative Analysis and Development of a Computer-aided System for Gastrointestinal Lesions Observed on Endoscopy

Keywords Gastrointestinal Endoscopy, Image Analysis, Computer-aided Diagnosis

Shigeto YOSHIDA

Department Hiroshima University Hospital

Title Assistant Professor

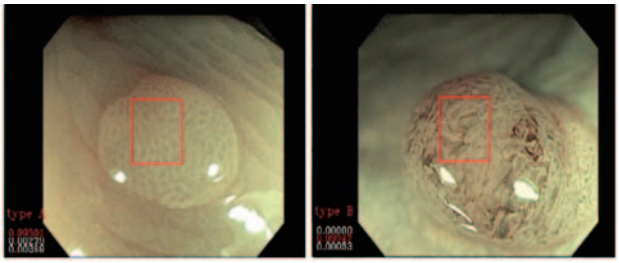
E-mail yoshida7@hiroshima-u.ac.jp

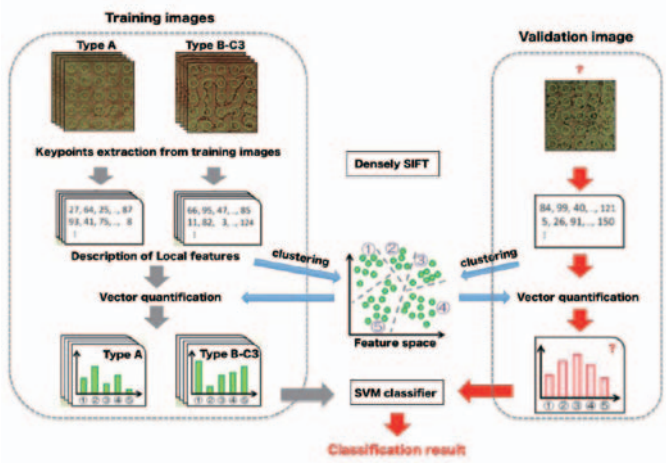
Field Clinical Internal Medicine, Biomedical Engineering, Informatics, Oncology

Outline

1. Background

Interpretation of endoscopic findings remains subjective and can vary among individual endoscopists. Although clinical training coupled with experience is a realistic approach to histologic prediction, a better approach would be objective evaluation of the classification criteria, such as computer-aided evaluation.





2. Research Summary

We used a “bag-of-features” representation of images for predicting histology. An image is represented by a histogram of visual words, produced by hierarchical k-means clustering of local features. We used a dense sampled scale-invariant feature transform descriptor as local features. The clustering is performed over all training images to generate k clusters (visual words). Scale-invariant feature transform descriptors are computed at points on a regular grid and at several scales of the local patch centered at each point. All descriptors of 128 dimensions are simply used by clustering. As a classifier, we used a support vector machine with linear kernel.

3. Result

The computer-aided classification system yielded a detection accuracy of 97.8%; sensitivity and specificity of neoplastic lesion were 97.8% and 97.9%, respectively. Our new computer-aided system is reliable for predicting the histology of colorectal tumors by using NBI magnifying colonoscopy.

4. For Application

Development of a computerized classification algorithm makes a simple-to- operate endoscopy system.
In addition these results will contribute to the high value-added endoscope system.

Competitive Advantages

Reports of image analysis of endoscopic images are few, and the computer-aided-diagnostics system is not developed. Our system is highly accurate and stable.

Patent/Journal/Award

Gastrointestinal Endoscopy, Journal of Gastroenterology

URL http://home.hiroshima-u.ac.jp/endosc/
http://home.hiroshima-u.ac.jp/gitract/

Life Science

Assessment of Oral and Pharyngeal Functions for Decision Making of the Ideal Thickness of Liquid

Keywords The Elderly, Prosthodontics, Swallowing Disorders

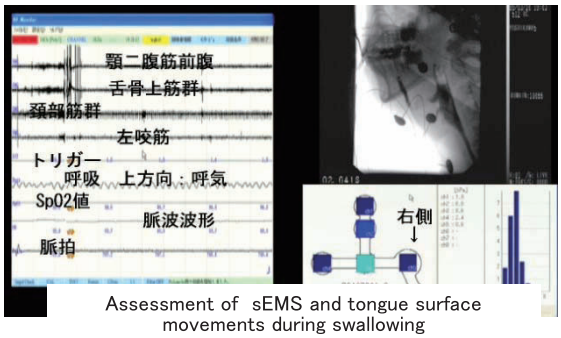
Mineka YOSHIKAWA
Department Institute of Biomedical & Health Sciences
Title Associate Professor
E-mail Professormineka@hiroshima-u.ac.jp Field Prosthodontics

Outline

1. Background

It's easy to cough or aspirate the liquid during swallowing in the elderly with swallowing disorders. Adding thickness to liquid is useful to avoid these situation, however, researches about thickness of liquid with physical assessments of swallowing function are rare and based on sensory or property assessments. In clinical situation, medical staffs decide the type and the amounts of thickening conditioners by their experimental rules. Making a new criteria and physical validation of "safe and easy to swallow" thickening liquid for swallowing disorder patients are needed.

Assessment of oral function by using JMS tongue pressure measurement device



Assessment of sEMS and tongue surface movements during swallowing

2. Research Summary

The relationship between oral/pharyngeal functions and test liquids with various thickness are assessed by using videofluorography, videoendoscopy, tongue pressure measurement, swallowing sounds, sEMS, sensory evaluation and so on in the healthy young people/elderly, the elderly with swallowing disorders.

3. Result

In young healthy people, the relationship between the swallowing duration time and thickness of liquid was found. However, there is likely to be no relationship between the results of sensory evaluation and swallowing function because of individualities even in healthy young people and the different tastes of thickness of liquid/solid. Data collection will be continued in the healthy elderly and dysphagic patients.

4. For Application

The results will contribute to the developments of special foods/liquids for the elderly with deteriorated swallowing functions in our super-aging society through swallowing assessments.

Competitive Advantages

The environment of the patients with swallowing disorders will be safer and more comfortable if the relationship between the oral/pharyngeal functions and ideal thickness of liquid are existed. We can contribute to the improvement of the problems in our super-aging society.

Patent/Journal/Award

Yoshikawa M, Yoshida M, Tsuga K, Akagawa Y, Groher ME. Comparison of three types of tongue pressure measurement devices. Dysphagia 2011; 26(3): 232–237.

Best poster award in the 19th annual conference of Japan society for mastication sciences and health promotion "Occlusal contacts and swallowing function"

"Development of easy-chew bread" in the 22nd annual conference of Japan society for mastication sciences and health promotion Symposium about "Easy- chew foods" (Oct, 2011)

URL

Life Science

Purification, Structure Characterization of Bioactive Substances from Marine Organisms and Application to Novel Anti-oral Cancer Drugs

Keywords Marine Organisms, Bioactive Substances, Anti-tumor Activity

Yukio YOSHIOKA

Department Institute of Biomedical & Health Sciences

Title Assistant Professor

E-mail yyosioka@hiroshima-u.ac.jp

Field Dentistry (Oral and Maxillofacial Surgery)

Outline

1. Background

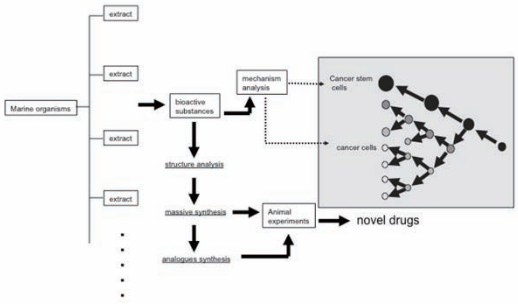
Marine organisms have some different systems of metabolism and physiological functions from the living things on the ground. We extract the bioactive substances from them and isolate the substances with the strong anti-tumor activity for the index of the cytotoxicity against cancer cells. We aim to apply them to the novel anti-tumor agents against oral cancer (collaborated with Prof. Ojika laboratory of Nagoya University).

soft coral

2. Research Summary

Marine organisms from Japanese adjacent sea are collected and freeze-dried. They are homogenized in EtOH-MeOH(4:1)and distributed by HPLC into hexane layer and $C_2H_5OCH_3CO$ layer and aqueous layer. Following it, the extracted compounds are investigated their activity by bio assay and are purified and decided their structure by LC/MS. Their analogues improving the structure of their branches are produced and massively synthesized them. The anti-tumor activity is investigated by the inoculated tumor cell on nude mouse.

The mechanism of the novel anti-tumor agents against not only the oral cancer but also the oral cancer stem cells is analyzed *In Vitro.*



3. Result

The native bioactive substance, *Spongolactam* isolated from the marine sponge living around the adjacent Okinawan Sea ,whose structure was similar to the farnesyltransferase, exhibited the anti-tumor effect. Many of its derivatives were produced and analyzed their anti-tumor effect *in Vitro*.

The analogues of asyrspermidine purified from the soft coral living in Okinawan Sea (see photograph) showed the strong anti-tumor effect against the cancer cells *in Vitro* and *in Vivo*.

4. For Application

Field of creating new drugs

This research can contribute to create not only anti-tumor agents but also the drugs for any other diseases.

Competitive Advantages

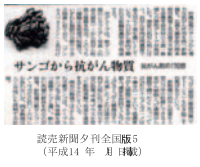
The novel compounds can be found in this study because the active biological substances are purified from the unlimited marine organisms and selected by the index of the cytotoxicity against the cancer cells and analyzed their structure with LC/MS.

Patent/Journal/Award

Patent; Application Number: PCT/JP2006/168926

Journal; Govindam V.S.S.,Yoshioka Y.,et al. Cyclolobatriene, a novel prenylated germacrene diterpene, from the soft coral *Lobophytum pauciflorum*. Bioorganic & Medicinal Chemistry 20 (2012) 687–692.

Report; This research was published at The *Yomiuri Shinbun* May 5 2002, The *Chugoku Shinbun* October 27 2001 (Right photograph).



URL

Life Science

Low Temperature Tolerance of Mammalian Transporters and Development of a New Transport Inhibitor

Keywords Transporter, Low Temperature Tolerance, Pan-inhibitor

Ryoko YUMOTO

Department Institute of Biomedical & Health Sciences

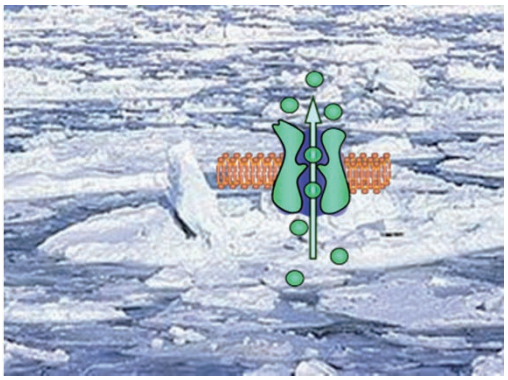
Title Assistant Professor

E-mail ryumoto@hiroshima-u.ac.jp Field Pharmaceutical Sciences

Outline

1. Background

The objective of this study is to clarify low temperature tolerance of human transporters. In addition, we have attempted to develop a new transport inhibitor.



2. Research Summary

The functionalities of human erythrocyte glucose transporter GLUT1 and nucleoside transporter ENT1 were examined at ice-cold temperatures using rightside-out membrane vesicles prepared from human erythrocytes.

3. Result

Our results indicate that human erythrocyte transporters GLUT1 and ENT1 function even at very low temperatures near 0°C. Therefore, in the absence of transport inhibitor in the stop solution, it was impossible to analyze the function of these transporters.

4. For Application

Industry (Research reagent)

Competitive Advantages

This study has provided a new concept for transporters. Development of pan-inhibitor of transporters would be a great help for the transport research in academia and pharmaceutical industries.

Patent/Journal/Award

1) Takano, M. Kimura, E., Suzuki, S. Nagai, J. and Yumoto R.: Human erythrocyte nucleoside transporter ENT1 functions at ice-cold temperatures. Drug Metab. Pharmacokinet., 25, 351–360 (2010)

2) Yumoto, R., Kimura, E., Suzuki, S., Imaoka, H. and Nagai, J. and Takano, M.: Transport characteristics of ribavirin in human erythrocyte membrane vesicles. Membrane, 34, 152–158 (2010)

URL

Researcher index

Keyword index

U

V

W

Y

Z

HIROSHIMA UNIVERSITY

Center for Collaborative Research & Community Cooperation

1-3-2 Kagamiyama Higashi-Hiroshima
Hiroshima 739-8511 Japan
TEL: +81-(0)82-424-4302
FAX: +81-(0)82-424-6189
E-mail: crcinter@hiroshima-u.ac.jp

2012.6