Welcome message

Wen-Yih Isaac Tseng
Director
National Taiwan University
Molecular Imaging Center

Dear Colleagues and Friends,

Welcome to the Biomedical Molecular Imaging 2015! We are pleased to have you join us in the famous resort of National Taiwan University in Xitou Education Area, and share with us your recent progress in biomedical and molecular imaging.

The conference is the 5th annual symposium of the National Taiwan University Molecular Imaging Center (NTU MIC). This annual symposium has been held since 2011, the establishment of NTU MIC, aiming to create networking opportunities for exchanging research results and to stimulate new ideas. We intend to hold the meeting in a resort area to help participants exchange ideas and form new research topics more effectively.

There are 83 people registered to attend the conference, and 29 posters will be presented. We have 23 invited speakers coming from Japan, USA and Taiwan. The speakers are world-leading scientists in a wide spectrum of disciplines including biomedical imaging, optical imaging, microscopy and spectroscopy.

I would like to thank all of you for your participation and sincerely hope that you will enjoy this three-day-event. I look forward to meeting with you during the meeting to further strengthen our ties for future cooperation.

Contents

Committee

Chair

Wen-Yih Isaac Tseng
Director, Molecular Imaging Center, National Taiwan University

Program Committee

Matthew Tirrell
Dean and Founding Pritzker Director of the Institute for Molecular Engineering, the University of Chicago
Sharon Feng
Senior Associate Dean for Budget and Strategy Contact, the Institute for Molecular Engineering, the University of Chicago
Hiro-o Hamaguchi
Chair Professor, College of Science, National Ciao Tung University
Chi-Kuang Sun
Distinguished Professor, Department of Electrical Engineering, National Taiwan University
Jyh-Horng Chen
Professor, Department of Electrical Engineering, National Taiwan University
Chung-Ming Chen
Professor, Institute of Biomedical Engineering, National Taiwan University
Ling-Wei Hsin
Associate Professor, School of Pharmacy, National Taiwan University
Kai-Yuan Tzen
Associate Professor, Department of Nuclear Medicine, National Taiwan University Hospital
Wei-Fang Su
Distinguished Professor, Department of Materials Science and Engineering, National Taiwan University
Chih-Yu Chao
Professor, Department of Physics, National Taiwan University
Pai-Chi Li
Distinguished Professor, Department of Electrical Engineering, National Taiwan University

Conference Secretary

Yuan Luo
Associate Professor, Institute of Medical Devices and Imaging, National Taiwan University

Organization Committee

Shi-Wei Chu
Professor, Department of Physics, National Taiwan University
Tzu-Ming Liu
Associate Professor, Institute of Biomedical Engineering, National Taiwan University
Ruoh-Fang Yen
Associate Professor, College of Medicine, National Taiwan University
Hwan-Ching Tai
Assistant Professor, Department of Chemistry, National Taiwan University
Jiashing Yu
Assistant Professor, Department of Chemical Engineering, National Taiwan University
Kung-Bin Sung
Associate Professor, Department of Electrical Engineering, National Taiwan University

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Organizer

Molecular Imaging Center, National Taiwan University, Taiwan
Taiwan Photonics Society

General Information

Symposium Venue

Xitou Education Area

55842 No.9, Senlin Lane, Lugu Township, Nantou County 558, Taiwan

TEL: +886-049-261-2111

Website: http://www.exfo.ntu.edu.tw/sitou/eng/01about/default.aspx

Registration & Tea Break

The Registration Desk will open from 13:00 am at 1F Lobby on Nov. 6th. Refreshments will also be served every tea break in the same area.

Internet Service

Education Center

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Log Cabin

66XX or N66XX：Connect to the internet directly

Red Building

XT_RedBuildingGuest：Klick the button "connect" after opening the browser

Oral Presentation

For invited speakers, you will have 15 minutes for presentation and Q&A. We will provide a laptop with Windows system, a projector, and a laser pointer for your convenience. In case you wish to use our computer, please kindly submit your file at the registration desk As Early As Possible (at least before your session starts). On the other hand, if you wish to use your own laptop, please be sure to check it's connection to the projector. Please feel free to contact us if you need any further assistance.

Poster Session

The poster size should not exceed 80cm*150cm (width*height) in PORTRAIT. Your poster number will be delivered and confirmed on the proceedings. Please follow the allocated number and tag your poster on the board at 1F Lobby. For each poster, at least one author is required to present during the poster session.

Poster Presentation Session

Each eligibility selected for Best Paper Awards will have 15 minutes for oral presentation and Q＆A. A laptop with Windows system, a projector, and a laser pointer are provided. Presenting the theme of the abstract via laptop on your own is allowed, too. Please contact us with your further inquiries if in need.

Awards

Best Paper & Poster Awards will be awarded in the closing ceremony on Nov. 8th, and the consequent are going to be announced on the website of Molecular Imaging Center.

Program of the Symposium

Fri., November 6th, 2015			
Time	**Schedule**		
08:30	Assembly Time		
08:30-09:00	**Roll Call (Breakfast Provided)*		
09:00-13:00	*Departure (Nameplate Given)* National Taiwan University→Xitou Nature Education Area		
13:00-14:20	**Registration & Lunch (Poster Gathered)*		
14:20-14:30	*Opening Ceremony*		
Time	**Title**	**Speakers**	**Chair**
14:30-14:45	Lecture 1 **White Blood Cell Discrimination by Raman Spectroscopy with Multivariate Curve Resolution Analysis**	Hiro-o Hamaguchi *National Ciao Tung University*	**Wen-Yih Isaac Tseng**
14:45-15:00	Lecture 2 **Wideband MRI and its applications**	Jyh-Horng Chen *National Taiwan University*	
15:00-15:15	Lecture 3 **Molecular Imaging Analysis to Investigate a Disease Animal Model of Cardiac Hypertrophy**	Ming-Fu Chang *National Taiwan University*	
15:15-15:30	Lecture 4 **Gene therapy for aromatic l-amino acid decarboxylase (AADC) deficiency**	Wuh-Liang Hwu *National Taiwan University Hospital*	
15:30-16:10	*Break & Check in (Professors)*		
16:10-16:25	Lecture 5 **A high throughput automatic analysis of brain fiber tracts: development and application**	Wen-Yih Isaac Tseng *National Taiwan University*	**Chin-Tu Chen**
16:25-16:40	Lecture 6 **Development of efficient capture techniques for molecular imaging of synaptic terminals**	Hwan-Ching Tai *National Taiwan University*	
16:40-16:55	Lecture 7 **Novel Fluoroalkyl-mitoxantrone Derivatives as Dual Molecular Imaging Agents for P-Glycoprotein Function**	Ling-Wei Hsin *National Taiwan University*	
16:55-17:10	Lecture 8 **Clinical PET Tracers beyond ^{18}F -FDG**	Ruoh-Fang Yen *National Taiwan University Hospital*	
17:10-17:40	*Check in (Students)*		
18:00-20:00	*Banquet*		
Sat., November 7th, 2015			
Time	**Schedule**		

07:30-08:30	*Breakfast*		
Time	**Title**	**Speakers**	**Chair**
09:00-09:15	Lecture 9 **New Frontiers in Polarized Light Microscopy for Live Cell Imaging**	Rudolf Oldenbourg *Marine Biological Laboratory*	**Tatsuyuki Yamamoto**
09:15-09:30	Lecture 10 **Chirality study of native collagen tissues based on second harmonic generation circular dichroism**	Shi-Wei Chu *National Taiwan University*	
09:30-09:45	Lecture 11 **Molecular Imaging of Bilirubin Dimers for Cancer Diagnosis**	Tzu-Ming Liu *National Taiwan University*	
09:45-10:00	Lecture 12 **Spatial-Spectral Holographic Fluorescence Microscopy**	Yuan Luo *National Taiwan University*	
10:00-11:00	***Break & Poster Session***		
11:00-11:15	Lecture 13 **New development of a Raman diagnosis for Eosinophil Esophagitis**	Tatsuyuki Yamamoto *Shimane University*	**Hiro-o Hamaguchi**
11:15-11:30	Lecture 14 **Development of Therapeutic Au-Methylene Blue Nanoparticles for Targeted Photodynamic Therapy of Cervical Cancer Cells**	Jiashing Yu *National Taiwan University*	
11:30-11:45	Lecture 15 **FDG-PET imaging cancer induced bone pain – related brain areas in mice**	Chen-Tung Yen *National Taiwan University*	
11:45-12:00	Lecture 16 **Biomedical Molecular Imaging in Tissue Engineering Research**	Wei-Fang Su *National Taiwan University*	
12:20-13:40	*Lunch*		
13:40-13:55	Lecture 17 **Non-invasive transpalpebral electrical stimulation improves retinal function in mice with photoreceptor degeneration**	Kin-Sang Cho *Harvard Medical School*	**Rudolf Oldenbourg**
13:55-14:10	Lecture 18 **Neurodifferentiation of Dental Pulps Stem Cells**	Min-Huey Chen *National Taiwan University*	
14:10-14:25	Lecture 19 **Organic Conductive Biomaterials for Neural Engineering**	Shyh-Chyang Luo *National Taiwan University*	
14:25-14:40	Lecture 20 **Resolving Sub-molecular Structure by**	Wanxin Sun *Bruker Corporation*	

	Scanning Probe Microscopy		
14:40-15:00	*Break*		
15:00-15:15	Lecture 21 **Computational Imaging for Molecular Characterization and Radiomics at the University of Chicago**	Chin-Tu Chen *The University of Chicago*	**Jyh-Horng Chen**
15:15-15:30	Lecture 22 **Exploring Biological Specimens with Focused Ion Beam**	Po-Kang Lin *Taipei Veterans General Hospital*	
15:30-15:45	Lecture 23 **The Framework of Pulmonary Image Registration Using Chest CT for Evaluation of Radiation-Induced Lung Disease (RILD)**	Chung-Ming Chen *National Taiwan University*	
15:50-16:00	***Poster Presentation Session***		
16:00-16:15	Student 1 **All-in-focus whole-brain microscopy for functional analysis**	Kuo-Jen Hsu *Department of Physics, National Taiwan University*	**Wei-Fang Su**
16:15-16:30	Student 2 **Talbot holographic illumination non-scanning fluorescence endoscopy**	Chen-Yen Lin *Institute of Medical Device and Imaging, National Taiwan University*	
16:30-16:45	Student 3 **The mechanism of nonlinear scattering of gold nanospheres**	Po-Ting Shen *Department of Physics, National Taiwan University*	
16:45-17:00	Student 4 **Non-scanning holographic light-sheet fluorescence microscopy for multi-plane imaging**	Xiaomin Zhai *Institute of Medical Devices and Imaging, National Taiwan University*	
17:00-17:15	Student 5 **High photo-stability, low saturation intensity organic light emitting device dye used in stimulated emission depletion microscopy**	Wei-Kuan Lin *Department of Physics, National Taiwan University*	
17:30-19:00	*Dinner*		
19:00	*Nighttime Sightseeing*		
Sun., November 8th, 2015			
Time	**Schedule**		
07:30-08:30	*Breakfast*		
Time	**Title**	**Speakers**	**Chair**
10:00-10:10	*Closing Ceremony & Check out*		
10:10-11:00	*Discussion*		
11:00	*Departure (Lunch Provided)* Xitou Nature Education Area→National Taiwan University		

Poster Presentation Titles

1

Capture-and-release strategy for single-synapse imaging and flow cytometry

Yi-Fong Zou, Hui-Ting Chen, Jia-Fong Jhou, Bo Y. Wang, Hwan-Ching Tai

2

Super Resolution STED Microscopy with Focus Extension

Kai-Ping Yang , Wei-Kuan Lin , Kuo-Jen Hsu , Shi-Wei Chu

3

Tissue Engineering for Resuscitation of Acute Optic Neuropathy

Chen-Hua Wang, Chun-Chih Ho, Po-Hsuen Chen, Ta-Ching Chen, King-Sang Cho, Dong-Feng Chen, Wei-Fang Su

4

Different Epileptic Brain Networks in Unilateral Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis Identified by the Whole Brain Tract-Based Automatic and Surface-based Analyses

Yao-Chia Shih, Hong-Huei Liu, and Wen-Yih Isaac Tseng

5

Improved image segmentation of voxel-based morphometry by constructing a group-specific tissue probability map

Yung-Chin Hsu, Wen-Yih Isaac Tseng

6

Individualized prediction of ADHD based on patterns of altered tract integrity over the whole brain: a performance test on adult female with ADHD using diffusion spectrum imaging

Yu-Jen Chen, Yun-Chin Hsu, Yu-Chun Lo, Shur-Fen Susan Gau, and Wen-Yih Isaac Tseng

7

Social communication network in high-functioning autism: a diffusion spectrum imaging (DSI) study

Yu-Chun Lo, Yu-Jen Chen, Susan Shur-Fen Gau, Wen-Yih Isaac Tseng

8

Group analysis of threshold-free cluster enhancement score with application to normal ageing white matter study by diffusion spectrum imaging

Pin-Yu Chen, Yu-Ling Chang, Yu-Jen Chen,Yu-Chun Lo, Yung-Chin Hsu, and Wen-Yih, I. Tseng

9

Exceptional Biocompatibility of Biodegradable Polyurethane / Cellulose Fibrous Scaffold for Cardiac Tissue Engineering

Wei-Fang Su, Chun-Chih Ho, Tzu-Hsiang Shih, Chen-Hua Wang, Chun-Hao Yeh

10

Visualization of AADC activity using 6-[^{18}F]fluoro-L-dopa (FDOPA) positron emission tomography (PET) on AADC deficiency mice under gene therapy

Chia-Hao Cheng, Ni-Chung Lee, Shin-Ichi Muramatsu, Kai-Yuan Tzen, Barry J. Byrne, Wuh-Liang Hwu

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Chu, Ann-Shyn Chiang
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The proliferation and differentiation of porcine adipose-derived stem cells by keratins incorporated with chitosan-Az
Yao-Chung Huang (黃耀樟), Chen-Yu Tsai (蔡鎮宇), Jiashing Yu (游佳欣)
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Data Driven 3D high-resolution structured illumination fluorescent microscopy based on Bayesian estimation
Hsi-Hsun Chen, Yuan Luo
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Fast wide-field optical sectioning microscopy with structured illumination for 3D tissue imaging
Wei Tang Lin, Chen Yen Lin, Yuan Luo
27
Incoherent digital volume holographic microscopy for 3D imaging
Po-Hao Wang, Hsi-Hsun Chen, Wei-Tang Lin, Yuan Luo
28
High photo-stability, low saturation intensity organic light emitting device dye used in stimulated emission depletion microscopy
Wei-Kuan Lin, Po-Fu Chen, Si-Han Wu, Jien-Chang Cheng, Hsueh-Yu Wu, Ken-Tsung Wong, Chung-Yuan Mou, and Shi-Wei Chu
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TBZ Derivatives as Potential PET Imaging Agent for Vesicular Monoamine Transporters
Zih-Rou Huang (黃梓柔), Ya-Yao Huang (黃雅瑤), Chyng-Yann Shiue (薛晴彥), Kai-Yuan Tzen (曾凱元), Ling-Wei Hsin (忻凌偉)

Introduction of Invited Overseas Speakers

Hiro-o Hamaguchi / Lecture 1

Chair Professor, College of Science, National Ciao Tung University

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The Hamaguchi Group, National Chiao Tung University
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Education and Professional Experience

1970 B. S. (Chemistry), The University of Tokyo
1975 D. Sc. (Chemistry), The University of Tokyo
1975 Research Associate, The University of Tokyo
1981 Lecturer, The University of Tokyo
1983 Associate Professor, The University of Tokyo
1990 Laboratory Head, Kanagawa Academy of Science and Technology
1995 Professor, Department of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo
1997 Professor, Department of Chemistry, School of Science, The University of Tokyo (Structural Chemistry)
2007-(present) Chair Professor, College of Science, National Chiao Tung University
2012-(present) Professor Emeritus, Department of Chemistry, School of Science, The University of Tokyo

Professional Service

International Journals

- Chemical Physics Letters（Elsevier), Editorial Advisory Board (1988-2008).
- Bulletin of the Chemical Society of Japan, Editorial Advisory Board (1988-1990).
- Laser Chemistry（Gordon & Bleach), Editorial Advisory Board (1992-2002).
- Chemical Physics（Elsevier), Editorial Advisory Board (1992-present).
- Journal of Raman Spectroscopy（Wiley), Associate Editor (1997-present).
- Chemistry Letters, Editorial Advisory Board (1997-2000).
- Applied Spectroscopy, Associate Editor for Japan (2000-2009).
- Journal of Molecular Structure (Elsevier), Editorial Advisory Board (2004-present).

International Conferences

- The KAST International Symposium on Time-resolved Spectroscopy (Kawasaki, 1991) Organizer.

- The 10th International Conference on Time-resolved Vibrational Spectroscopy (Okazaki, 2001) Co-chair.
- The 20th International Conference on Raman Spectroscopy (Yokohama, 2006) Chair.
- The 2nd International Congress on Ionic Liquids (Yokohama, 2007) Co-chair.
- Advanced Spectroscopy and Imaging in Molecular Science (Hsinchu, Taiwan, 2010) Co-chair.

Steering Committee Membership of International Conferences

- International Conference on Time-resolved Vibrational Spectroscopy
- Laser Applications in Life Sciences
- International Conference on Raman Spectroscopy (2006-present, Steering Committee Chairman 2008-2010)
- Asian Conference on Spectroscopy(2007-present, Steering Committee Founding Chairman)
- European Congress on Molecular Spectroscopy(2008-present)
- CODATA Executive Committee member (2010-present)

Others

- Director of the Chemical Society of Japan, 2000-2002
- President of the Spectroscopical Society of Japan, 2003-2005

Honors and Awards

- Ramasay Fellow, 1977-79
- Pittsburgh Conference Lectures, 1993
- Meggers Award, Society for Applied Spectroscopy, 2005
- The Spectroscopical Society of Japan Award, 2006
- The Chemical Society of Japan Award, 2009
- TRVS (Time-resolved Vibrational Spectroscopy) Award, 2009
- Fellow of the Society for Applied Spectroscopy USA, 2010

Rudolf Oldenbourg / Lecture 9
Senior Scientist, the Eugene Bell Center, the Marine Biological Laboratory
~~Phone (508) 289-7426~~
~~Fax (508) 289-7900~~
E-Mail rudolfo@mbl.edu
Address MBL, 7 MBL Street, Woods Hole, MA 02543
Laboratory of Rudolf Oldenbourg
http://www.mbl.edu/bell/current-faculty/oldenbourg-lab/

RESEARCH INTERESTS:

Our research is inspired by advanced optical methods to study the architectural dynamics in living cells. We are developing a new type of polarized light microscope, the LC-PolScope, for the analysis of molecular order directly in living cells with unprecedented sensitivity, resolution, and speed. Based on polarization measurements, we gain insight into submicroscopic structural parameters and non-invasively create contrast where native structures are otherwise invisible. We seek interdisciplinary collaborations to conduct research in physical optics for the interpretation of image content and in computational methods for image enhancement and restoration. These physical and engineering projects are stimulated and guided by biological inquiries into the structural basis of cell function.

LAB PROJECTS:

– OpenPolScope
– Polarized Light Field Imaging
– Imaging @ MBL

Tatsuyuki Yamamoto / Lecture 13
Faculty of Life and Environmental Science, Department of Life Science and Biotechnology, Shimane

Degree
Dr. Science (The University of Tokyo), Master of Science(The University of Tokyo)
Major
Biophysical Chemistry
Educational record
April, 1981　Entered the University of Tokyo, College of Arts and Sciences
March, 1985　Graduated from the same, department of chemistry, Faculty of Science
April, 1985　Entered Master course of chemistry, graduate school of Science, the University of Tokyo
March, 1987　Graduated from the same
April, 1987　Advanced to Doctor course of the same
March, 1990　Graduated from the same
March, 1990　Doctor of Science Hakuri No.2249, The University of Tokyo
Employment record
April, 1990～June, 1990　Assistant professor of the Tokyo Institute of Technology, Faculty of Science
June, 1990～January, 1997　Assistant professor of the same, Faculty of Bioscience and Biotechnology
January, 1997～October, 2004　Associate professor of Shimane University, Faculty of life and Environmental science
October, 2004～present　Professor of Shimane University, Faculty of Life and Environmental Science
February, 2014～present　Director of Raman Project Center for Medical and Biological Applications of Shimane University
April, 2014～present　Project Leader of the project research of Shimane University
“Establishment of a cross-disciplinary hub center to develop unique medical technologies”
Awards
March, 2007　BCSJ awards (Chemical Society of Japan)
Research Interest
Biomedical application of Raman spectroscopy
Molecular spectroscopic study on the effect of ultra violet radiation, oxidative stress on living tissues and cells
Biomedical applications of inclusion complexes

Kin-Sang (Anson) Cho, Ph.D. / Lecture 17
Investigator, Schepens Eye Research Institute
Instructor, Harvard Medical School
~~Contact~~
~~617-912-7415~~
~~FAX: 617-912-0101~~
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Education
Ph.D., The University of Hong Kong

Research Story
The research of Dr. Kin-Sang (Anson) Cho has been focused on why neurons in the Central Nervous System (CNS) cannot re-grow in adult mammals. Visual system has been used as a model to study CNS regeneration. The expression pattern of Bcl-2 had been shown to correlate to the decline of intrinsic growth ability of retinal ganglion cells (CNS neurons inside retina) during development. In addition, he has demonstrated that over-expressing Bcl-2 could maintain the intrinsic growth ability over growth-inhibitory substrates in culture.

Dr. Cho further explored to find out if the over-expression of Bcl-2 is sufficient to support long distance regeneration of optic nerve from the eye to the brain *in vivo*. He found that over-expressing Bcl-2 in transgenic mice supported robust axon regeneration following optic nerve crush on postnatal day 3 (P3), but not in later stage. Next, the mechanisms causing the failure of optic nerve regeneration occurs in mature Bcl-2tg mice were explored. Dr. Cho discovered that the CNS environment expresses growth inhibitory molecules, at P5 or later, that block axonal regeneration *in vivo* and in vitro.

Many studies have suggested that CNS glial cells, including astrocytes and oligodendrocytes/myelin, may contribute to the growth inhibitory effect in the CNS environment. By examining glial cell development in mouse brains, Dr. Cho has demonstrated that the maturation of astrocytes, rather than myelin, correlates to the onset of growth inhibitory mechanism in the CNS at P5. Maturation of astrocytes seems to play a critical role in preventing CNS regeneration. This hypothesis was tested by administration of the specific toxin, L-aminoadipate, against astrocytes in optic nerve of adult Bcl-2 transgenic mice. The result showed that L-aminoadipate could eliminate a majority of astrocytes and allow extensive axonal regeneration into the astrocyte-free area. Instead of using Bcl-2 transgenic mice, Bcl-2 can be induced in neurons of wild-type mice by feeding them with lithium-containing food. In combination with lithium-containing food and L-aminoadipate, this approach could induce the severed optic nerve to regenerate in wilt-type adult mice.

The role of astrocytes in suppressing optic nerve regeneration was further confirmed in a genetic mouse model of which the scar forming activity of astrocytes is suppressed – mice deficient in astrocyte intermediate filament proteins, glial fibrillary acidic protein (GFAP) and vimentin. Dr. Cho generated the triple mutant mice by crossing Bcl-2tg mice to GFAP/Vimentin double knockout

mice (G/VKO). In theory, neurons in these triple mutant mice maintain their intrinsic capacity to grow axons, while their astrocytes present less scar formation following injury. Dr. Cho's data showed that robust optic nerve regeneration occurred in the triple mutant mice following optic nerve crush after P5 and that regenerating axons reached their visual targets in the brain. This is the first report that a high proportion of RGC axons regenerate after injury over a long distance into the brain targets.

Taken together, the results suggest that the expression of Bcl-2 in neurons and the suppression of scar formation in CNS are crucial for robust CNS regeneration in adult mammals. Dr. Cho's study provides insights that will be helpful in developing new strategies to treat CNS injury.

Chin-Tu Chen / Lecture 21
Associate Professor of Radiology
Committee on Medical Physics and the College
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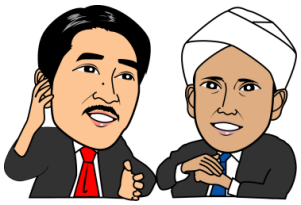
Research Summary
Functional and physiological imaging, molecular imaging, PET/CT, SPECT/CT, multi-modality imaging and image integration, quantitative image analysis, nuclear medicine imaging, and image reconstruction.

Education
1974 B.S. (Physics), National Tsing-Hua University, Hsinchu, Taiwan
1978 M.S. (Physics), Northwestern University, Evanston, Illinois, USA
1986 Ph.D. (Medical Physics), The University of Chicago, Chicago, Illinois, USA

Professional Experience
4/1/82 - 12/31/86 Physicist, The Franklin McLean Memorial Research Institute and Department of Radiology, The University of Chicago, Chicago, Illinois.
1/1/87 - 6/30/87 Research Associate (Instructor), Department of Radiology, The University of Chicago
4/1/87 - present Director, Frank Center for Image Analysis, Department of Radiology, The University of Chicago
7/1/87 - 6/30/94 Assistant Professor, Department of Radiology and Graduate Program in Medical Physics, The University of Chicago
7/1/87 - present Fellow, Brain Research Institute, The University of Chicago
7/1/94 - present Faculty Member, Cancer Research Center, The University of Chicago
7/1/94 - present Associate Professor, Department of Radiology and Committee on Medical Physics, The University of Chicago
7/1/05 – present Director, Functional and Molecular Imaging Core, Bio

Professional Associations
American Association of Physicists in Medicine (AAPM)
Society of Nuclear Medicine (SNM)
The Institute of Electrical and Electronics Engineering (IEEE)
American Association for the Advancement of Sciences (AAAS)
The International Society for Optical Engineering (SPIE)
Academy of Molecular Imaging (AMI) Society of Molecular Imaging (SMI)

Abstracts for Oral Presentation



Lecture 1

White Blood Cell Discrimination by Raman Spectroscopy with Multivariate Curve Resolution Analysis

Masahiro Ando[1] and Hiro-o Hamaguchi[1,2]

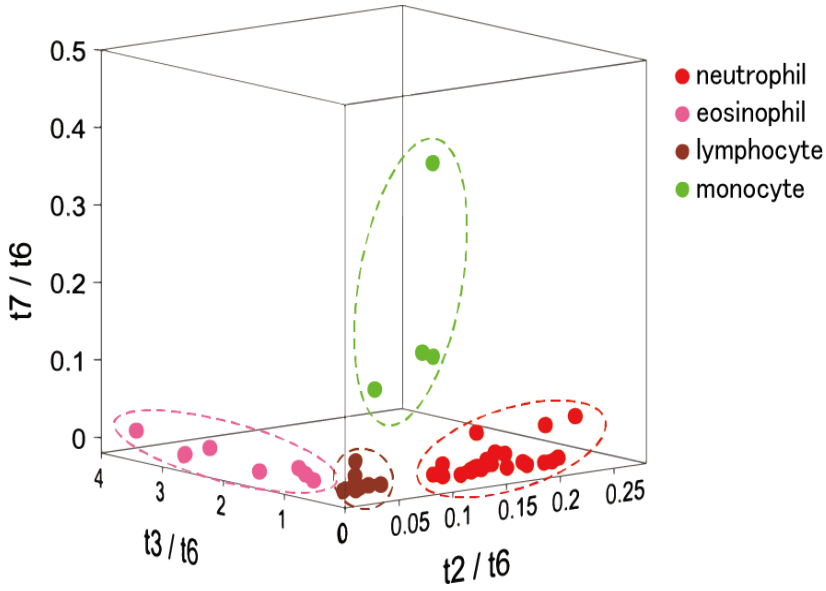
[1]*Research Organization for Nano & Life Innovation, Waseda University, 513 Wasedatsurumaki-cho, Shinjuku, Tokyo, 162-0041 Japan*

[2]*Institute of Molecular Science and Department of Applied Chemistry, National Chiao Tung University, 1001 Ta Hsuch Road, Hsinchu 300, Taiwan*

E-mail: hhama@nctu.edu.tw

Abstract

We use the multivariate curve resolution-alternating least squares (MCR-ALS) analysis for automatic and objective *in vivo* living cell discrimination by Raman spectroscopy. We apply the MCR-ALS analysis to a total of 10400 Raman spectra of white blood cells (400 Raman spectra from 26 different leukocyte; 12 neutrophils, 5 eosinophils, 6 lymphocytes, and 3 monocytes) to obtain eight chemically interpretable spectra S-1 to S-8 and their spatial distributions. S-1 is ascribed to nucleus (nucleic acids + proteins), S-2 myeloperoxidase (MPO), S-3 eosinophil peroxidase (EPO), S-4 lipids, S-5 carotenoids, S-6 proteins in cytoplasm, S-7 proteins + MPO and S-8 water. The plot of the contributions of S-2, S-3 and S7 relative to S-6 is shown in Figure 1.The four different types of white blood cell are clearly discriminated. Now that we have established the principal MCR spectral components in white blood cells, any new sample cell can be analyzed automatically and objectively for fast *in vivo* discrimination.



Fig~~ure~~. 1. Contribution scatter plot of MCR-ALS retrieved component 2, 3, and 7 for the discrimination of four types of leukocytes: neutrophils (red), eosinophils (pink), lymphocytes (brown), monocytes (green).

Lecture 2

Wideband MRI and its applications

Jyh-Horng Chen
National Taiwan University
E-mail: jhchen@ntu.edu.tw

Abstract

Among the most important medical imaging technologies, magnetic resonance imaging (MRI) provides abundant anatomical information as well as physiological *in vivo* data, revealing microscopic as well as macroscopic features of biological tissue. However, MRI suffers from the limitations of relatively long scanning time and low resolution, when compared to other imaging techniques such as computer tomography (CT).

To meet the increasing demand and expanding the possibilities of such a versatile imaging modality, we have developed Wideband MRI techniques as a means of significantly increasing the speed of both 2D & 3D MR imaging process. Through sequence design and adequate signal processing, 2D & 3D images with higher spatial/temporal resolutions could be obtained without compromise.

Routine usage of Wideband MRI can reduce scan times to between 1/2 and 1/8 the time currently required. From real-time biological information to functional imaging, the improved temporal/spatial resolution provided by Wideband MRI technology enables a wide variety of applications never before envisioned, and paves the way for fast whole-body early-stage cancer screening in the near future.

This presentation will introduce various Wideband MRI applications, showing the potentials of higher spatial/temporal resolutions in imaging and the possibilities that it may bring to clinical applications, scientific research and molecular imaging as well.

Lecture 3

Molecular Imaging Analysis to Investigate a Disease Animal Model of Cardiac Hypertrophy

Ming-Fu Chang[1], Linda Tzu-Ling Tseng[1], Chieh-Liang Lin[1], Kai-Yuan Tzen[2], Pai-Chi Li[3] and Shin C. Chang[4]

Institute of Biochemistry and Molecular Biology[1], and Institute of Microbiology[4], College of Medicine, National Taiwan University, and the Department of Nuclear Medicine[2], National Taiwan University Hospital, Department of Electrical Engineering[3], National Taiwan University, Taipei, Taiwan.

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Abstract

Clathrin-mediated endocytosis is a major pathway for receptor internalization, which is essential for both the recycling of proteins and receptors on the plasma membrane (PM) and the intracellular signaling. The insulin receptor (IR) is a receptor tyrosine kinase that controls mammalian growth and maintains the homeostasis of lipid and glucose metabolism. When insulin binds to the IR, it amplifies insulin signals by stimulating a structural change in the IR, allowing the activation of its tyrosine kinase activity and the downstream PI3K/Akt pathway, resulting in the translocation of glucose transporter 4 from the cytoplasm to the PM for glucose uptake and metabolism. IR signaling is terminated through receptor-mediated endocytosis followed by the action of tyrosine phosphatase PTP1B in the endosomal compartments. Although the juxtamembrane dileucine motif of the IR is essential for AP2-clathrin-mediated endocytosis, the adaptor protein that specifically regulates the internalization of the IR remains unidentified. Our recent studies demonstrated that PM-localized LMBD1 protein functions as a specific adaptor for the clathrin-mediated endocytosis of the IR through its interaction with AP-2. Because cargoes are internalized in a non-competitive, non-saturable manner, cargo selectivity is observed. LMBD1 is not involved in the transferrin receptor endocytosis. Whereas, molecular mechanisms and the specificity of LMBD1 involved in the IR endocytsis are not fully understood. In this study, we found that the lmbrd1$^{+/-}$ mice exhibited a significant elevation of myocardial glucose uptake and increases in heart rate, cardiac muscle contractility and ventricular wall thickness. In addition, PI3K inhibitor Wortmannin inhibited the cardiac glucose uptake in the lmbrd1$^{+/-}$ mice. Collectively, *lmbrd1* heterozygous knockout results in a constitutive activation of insulin receptor-PI3K-Akt signaling and the development of cardiac hypertrophy and fibrosis in mice.

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Lecture 4

Gene therapy for aromatic l-amino acid decarboxylase (AADC) deficiency

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Abstract

Aromatic l-amino acid decarboxylase (AADC) is an enzyme responsible for the final step of the synthesis of neurotransmitters dopamine and serotonin. AADC deficiency is a rare genetic disorder causing motor and autonomic dysfunction and early death in children. Taiwanese carry a high prevalence of AADC deficiency due to a founder mutation (IVS6+4A>T) in the AADC gene. In the past few years, we conducted both a human gene therapy trial with local injection, and mouse studies with wide spread vectors. In both categories, [^{18}F]fluoro-dopa positron emission tomography (FDOPA PET), play a major role in the evaluation of gene expression. We previously created an IVS6+4A>T knock-in mouse model of AADC (Ddc^{KI} mice). We first showed that gene therapy with direct intraventricular injection of AAV9-CMV-hAADC (AAV9-AADC) at the neonatal stage can rescue the phenotype. We then extended the treatment to systemic therapy on young mice. After intraperitoneal injection of 7-day-old mice with either AAV9-CMV-hAADC (AAV9-AADC) or yfAAV9/3-Syn-I-mAADC (AAVN-AADC), the treated Ddc^{KI} mice showed improvements in weight gain, survival, motor function, autonomic function, and behavior, but the effects of AAVN-AADC were superior. Moreover, the AAV9-AADC-treated Ddc^{KI} mice exhibited slight hyperactivity. Under low magnification, AADC-positive cells were found in the cortex of AAV9-AADC-treated mice. Therefore, mice with a neurotransmitter deficiency can be rescued at a young age using systemic gene therapy, but a neuron-specific vector may be necessary. A gene therapy with recombinant adeno-associated virus (AAV) serotype 2 CMV promoter-driven human AADC (AAV2-hAADC) was conducted in children with AADC deficiency since 2010. Clinical grade vector was manufactured. All patients, except one, had homozygous IVS6+4A>T mutations. PET signal intensity over putamen increased and cerebrospinal fluid neurotransmitter levels rose in all treated patients. There is no virus-associated side effect, and currently no patient reveals a loss of treatment effect. Currently, a new Phase I/II clinical trial is ongoing.

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Lecture 5

A high throughput automatic analysis of brain fiber tracts: development and application

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Abstract
Connectome is a comprehensive map of neuronal connections in the brain. Diffusion MRI is the only imaging tool that can acquire such information from living human brain noninvasively. Diffusion MRI measures water molecular diffusion at the microscopic scale. The signal of diffusion MRI carries information about the microscopic structures, one of which is the orientation of the axonal fibers. Knowing axonal fiber orientation at each pixel location, one can apply a tractography technique to reconstruct fiber tracts. The fiber tracts reconstructed by tractography have been validated to correspond to the axonal fiber tracts revealed by invasive trace injection study. Since axonal fibers are the extension of neurons by which neurons connect to other neurons at distant location in the brain. Connectome can be obtained by reconstructing fiber tracts between any two brain regions, quantifying the strength of structural connection between the two regions in terms of number of a connectivity index. This approach, however, is usually done manually, and therefore is operator dependent and time consuming. Here, we propose an automatic analysis of the whole brain fiber tracts. This method is achieved by two key developments: a diffusion MRI template and a tract atlas. For each tract entity, connectivity index is sampled along the tract step by step. The sampling process is performed along all tract entities of the brain to obtain multiple sampling profiles. These sampling profiles can be normalized by the same number of sampling steps, and they can be displayed as a 2D map. In this 2D map, each row represents a sampling profile of a tract entity, and each column represents the microstructural property of all tract entities at the same step location. Such format can be considered as a 2D array of brain connectome and can be used as a platform for databank collection, opening an avenue for big data mining in the search of biomarkers. We have applied this automatic method to various neuropsychiatric diseases such as schizophrenia, autism spectrum disorder, attention deficit hyperactivity disorder, epilepsy, and Alzheimer's disease. We found characteristic patterns of impaired tract integrity corresponding to different diseases. Some of the patterns may serve as imaging biomarkers for early diagnosis or prediction of prognosis.

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Lecture 6

Development of efficient capture techniques for molecular imaging of synaptic terminals

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Abstract

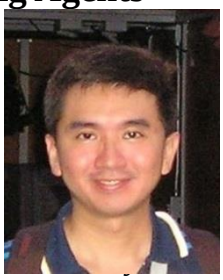
The study of synapses has been a central focus of neuroscience since the time of Cajal. Our laboratory is interested in understanding disease-associated synaptic changes in the human brain and drug-induced synaptic changes in animal models for pharmacological development. Although the isolation method of synaptic terminals from brain tissues is well established, there is still much technical difficulty in conducting immunofluorescence staining on such tiny organelles because conventional protocols based on repeated sedimentation work poorly.

We have developed an efficient method to capture synaptosomes (pinched-off synaptic terminals) onto glass slides so that they can be immunostained and imaged just like fixed cultured cells, albeit being much smaller. Fixation of synaptosomes in suspension is conducted with ethylene glycol bis(succinimidyl succinate) (EGS), which not only crosslinks proteins by via their amine groups, but also makes the surface of synaptosomes more negatively charged. This facilitates the adhesion of synaptosomes to positively charged glass surfaces modified by (3-aminopropyl)triethoxysilane (APTES) via electrostatic attraction.

We found that electrostatic attraction is much more effective in capturing synaptosomes compared to several variations of avidin-biotin binding strategies previously developed in our lab. Moreover, the increase of negative surface charges due to EGS fixation prevents the aggregation of synaptosomes via electrostatic repulsion, compared to paraformaldehyde fixation previously used in our lab. So this new technique is ideal for imaging individual synapses isolated from brain tissues, and we are currently trying to conduct super-resolution imaging of beta amyloid and tau protein to understand their localization within synaptic terminals. The interaction of these two proteins at the synapse may be very important for understanding the pathogenesis of Alzheimer's disease, and our improved method for capturing synaptosomes will facilitate such investigation.

Lceture 7

Novel Fluoroalkyl-mitoxantrone Derivatives as Dual Molecular Imaging Agents for P-Glycoprotein Function



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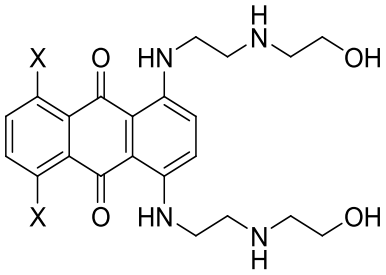
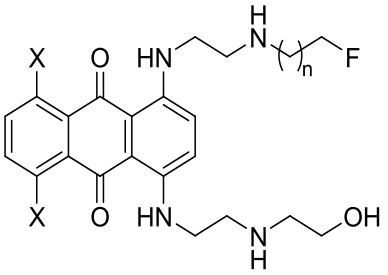
Abstract

Overexpression of P-glycoprotein (P-gp), an ATP-binding cassette (ABC) transporter, is one of the most common mechanisms to multidrug resistance (MDR), which is one of the major obstacles in cancer chemotherapy. Therefore, an molecular imaging agent that could quantitatively and sensitively measure the *in vitro* and *in vivo* levels of P-gp expression and activity would be valuable for predicting the outcome of cancer chemotherapy for individual patient, and development of novel anti-cancer drugs and chemotherapeutic treatment strategies. Since mitoxantrone (MX) is a well-known substrate for P-gp, a series of fluoroalkyl-substituted 1,4-bis[(2-aminoethyl)amino]anthraquinone derivatives 1 was designed and synthesized as potential P-gp function imaging agents for fluorescence and positron emission tomography (PET). Compounds 1 could accumulate in P-gp-deficient cancer cells in compare with P-gp-highly-expressed cancer cells, and these ligands also possessed much weaker DNA binding ability and much less cytotoxicity against cancer cells than MX. Thus, these novel ligands demonstrated the potential to be molecular imaging probes for P-gp function, and ^{18}F-labeled compound 1 was radio-synthesized for the development of novel P-gp radiotracer for positron emission tomography.



Ametantrone (**AT**): X = H
Mitoxantrone (**MX**): X = OH



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Lecture 8

Clinical PET Tracers beyond ^{18}F-FDG

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Abstract

^{18}F-FDG, a glucose analog, which substitutes a fluorine atom for the hydroxyl group at C-2 on glucose, is a useful radiopharmaceutical for measuring *in vivo* biodistribution of glucose metabolism. It has been widely used in diagnosis, staging and follow-up of several malignancies. In addition, there are several other PET probes, such as ^{18}F-NaF for bone metastases, ^{18}F-fluorothymidine and ^{18}F-fluorocholine for cell proliferation, ^{18}F-fluordopa for dopaminergic neuron integrity and neuroendocrine tumors, etc. In addition, there are brain imaging tracers, including ^{11}C-PIB for β-amyloid, T-807 for tau protein, ^{18}F-fallypride for D2 receptor, etc. I would give an introduction on the PET tracers available at present in NTUH PET and Cyclotron center.

Lecture 9

New Frontiers in Polarized Light Microscopy for Live Cell Imaging

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Abstract

Polarization is a basic property of light that is often overlooked, because the human eye is not sensitive to polarization. Therefore, we don't have an intuitive understanding of it and optical phenomena that are based on polarization either elude us or we find them difficult to comprehend. Meanwhile, polarized light plays an important role in nature and can be used to manipulate and analyze materials, including living cells, tissues and whole organisms, by observing them with the polarized light microscope.

At the Marine Biological Laboratory, we are developing polarized light imaging techniques that employ new optical components and configurations, and rely on new acquisition and processing algorithms for generating time-lapse images that clearly reveal the architectural dynamics of molecular assemblies in organelles, cells, and tissues.

We created the LC-PolScope, a modern polarized light microscope, by enhancing the traditional microscope with liquid crystal devices, electronic imaging and digital image processing techniques to reveal and measure the alignment of molecules over the whole field of view at once [1]. In recent years we expanded the LC-PolScope technique to include the measurement of polarized fluorescence of GFP and other fluorescent molecules, and applied it to record the remarkable choreography of septin proteins during cell division, displayed in yeast to mammalian cells [2].

Polarization analysis in microscopy combines the exquisite morphological detail available in modern microscope images with the submicroscopic resolution available with polarization analysis that reveals the alignment of molecular bonds, of fine structural form, and of fluorescent dipoles. Polarized fluorescence further combines the molecular specificity available with fluorescent labeling with the structural specificity afforded by polarization analysis. In fact, most if not all contrast methods in light microscopy, when coupled with polarization analysis, can reveal new, vital information about the architectural dynamics in living cells, tissues, and man-made materials.

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Lecture 10

Chirality study of native collagen tissues based on second harmonic generation circular dichroism

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Abstract
Chirality plays a fundamental role in biomedical fields; many drugs, enzymes, and biomolecules cannot function unless their chiralities are correct. Since the conformation of a molecule, as well as the chirality, is very sensitive to the local microenvironment, it is vital to characterize molecular chirality without altering the surrounding conditions. To determine the chirality in materials, optical activity is the most common way. In linear optics, optical rotatory dispersion and circular-dichroism are the two well-developed methods for probing chirality. However, their weak contrast, poor optical sectioning, and low penetration depth constrain its application to study chirality in tissues and real bio-samples. Therefore, previous research has been mostly limited to surfaces or solutions.

In contrast to linear optics, there are several nonlinear optical activity effects in chiral materials, such as vibrational circular dichroism, Raman optical activity, two-photon absorption circular dichroism, and second-harmonic generation circular-dichroism (SHG-CD). The last one is the most studied nonlinear chiral effect since it shows significantly improved chiral contrast. An additional advantage of SHG-CD is its intrinsic optical sectioning due to nonlinearity. When combined with an infrared excitation, SHG-CD has been demonstrated to provide high penetration depth for three-dimensional imaging. However, in recent studies, the signal origin of SHG-CD in biological tissue is ambiguous, since not only chirality, but also the anisotropy of molecules contribute to SHG-CD response. It will be of great importance to find an experimental skill that can distinguish the contribution between these two mechanisms.

Here we studied SHG-CD of collagen, which is the most abundant protein in human body. Inspired by linear CD where resonant wavelength is required to reveal chirality, we have carried out nonlinear microspectroscopy measurement and shown that when the excitation meets the resonant band of collagen, chirality-induced SHG-CD is strongly enhanced and can be easily identified versus the anisotropy-induced contribution. By slowly heating up the sample, we have further verified that there is a wavelength-independent anisotropy contribution of SHG-CD vanishing at around 40 – 50 degree Celsius, while the resonance-enhanced chirality component of SHG-CD remains until temperature rise to 60 degree. Our results feature the first quantitative identification of chirality-induced SHG-CD in an intact biological tissue, and will be a critical step toward nonlinear chiral microscopy.

Lecture 11

Molecular Imaging of Bilirubin Dimers for Cancer Diagnosis

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Abstract

Based on an infrared femtosecond Cr:forsterite laser, we developed a molecular imaging method of bilirubin dimers. At the wavelength of 1230nm, we selectively excited the two-photon red fluorescence of bilirubin dimers around 660 nm. Autofluorescences from other endogenous fluorophores were greatly suppressed. The molecular specificity of red fluorescence was further validated by a mass spectroscopy measurement. Using this distinct fluorescence measure, we found that poorly-differentiated hepatocellular carcinoma (HCC) tissues on-average showed 3.7-times lower concentration of bilirubins than the corresponding non-tumor parts. This feature can be used to define the boundary of HCC in the surgery. The fluorescence lifetime imaging microscopy measurements indicated that HCC tissues exhibited a longer lifetime (500 ps) than those of non-tumor parts (300 ps). Similarly, oral cancer cell lines had longer lifetimes (>330 ps) than those of non-tumor ones (250 ps). We anticipate the developed methods of bilirubin molecular imaging to be useful in diagnosing cancers or studying the dynamics of bilirubin metabolisms in live cells.

Lecture 12

Spatial-Spectral Holographic Fluorescence Microscopy

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Abstract

Laser induced fluorescence has been developed for a variety of clinical applications. However, many of the existing biomedical imaging systems typically require scanning in two lateral dimensions as well as depth focusing. Efforts to improve scanning efficiency by optimizing the scanning algorithm or increasing the number of focal points are ongoing. However, these methods can increase system complexity and do not eliminate the need for moving parts. This talk will introduce volume holographic imaging systems to acquire spatial images with spectral selectivity and no scanning in both transverse and longitudinal directions. The imaging modality is based upon multiplexed volume holographic (MVH) gratings acting as spatial-spectral filters used in an optical imaging system. In addition, with proper multiplexed holographic pupil engineering, the MVH systems can obtain multiple depth-resolved phase-contrast imaging in real-time in a single shot. Moreover, the talk will address MVH techniques incorporating other state-of-the-art imaging methods to better manipulate light for imaging in a variety of applications.

Lecture 13

New development of a Raman diagnosis for Eosinophil Esophagitis

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Abstract

As reported last year, we have already succeeded in detecting eosinophils invaded into the inner membrane of esophagus of model mice, which artificially occurred Eosinophil Esophagitis by repeated injection of interleukin-33[1]. –In some mouse tissues of treated mouse esophagus, the Raman bands due to eosinophil peroxidase unique to eosinophils were detected. –The invasion of eosinophils into these tissue was confirmed by checking the optical images of the same tissues dyed by HE, after Raman measurements. —The aim of our study is to develop a new Raman probe system, which can be used as an option probe for an endoscope. –For this purpose, we have tested a model human eosinophil esophagitis tissue, prepared by human esophagus membrane with exceeded amount of separated human white blood cells involving eosinphil. –Using this model tissue, we are now trying to develop an optical fiber Raman probe with a diameter smaller than an inner tube of a commercially available endoscope. –We will report on our recent results for such approaches.

Reference:

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Lecture 14

Development of Therapeutic Au-Methylene Blue Nanoparticles for Targeted Photodynamic Therapy of Cervical Cancer Cells

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Abstract

Photodynamic therapy (PDT) involves the cellular uptake of a photosensitizer (PS) combined with oxygen molecules and light at a specific wavelength to be able to trigger cancer cell death via the apoptosis pathway, which is less harmful and has less inflammatory side effect than necrosis. However, the traditional PDT treatment has two main deficiencies: the dark toxicity of the PS and the poor selectivity of the cellular uptake of PS between the target cells and normal tissues. In this work, methylene blue (MB), a known effective PS, combined with Au nanoparticles (NPs) was prepared using an intermolecular interaction between a polystyrene-alt-maleic acid (PSMA) layer on the Au NPs and MB. The Au@polymer/MB NPs produced a high quantum yield of singlet oxygen molecules, over 50% as much as that of free MB, when they were excited by a dark red light source at 660 nm, but without significant dark toxicity. Furthermore, transferrin (Tf) was conjugated on the Au@polymer/MB NPs via an EDC/NHS reaction to enhance the selectivity to HeLa cells compared to 3T3 fibroblasts. With a hand-held single laser treatment (32 mW/cm) for 4 min, the new Au@polymer/MB-Tf NPs showed a two-fold enhancement of PDT efficiency toward HeLa cells over the use of free MB at 4 times dosage. Cellular staining examinations showed that the HeLa cells reacted with Au@polymer/MB-Tf NPs and the 660 nm-light excitation triggered PDT, which caused the cells to undergo apoptosis ("programmed" cell death). We propose that applying this therapeutic Au@polymer/MB-Tf nanoagent is facile and safe for delivery and cancer cell targeting to simultaneously minimize side effects and accomplish a significant enhancement of the photodynamic therapeutic efficiency towards next-generation nanomedicine development.

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Lecture 15

FDG-PET imaging cancer induced bone pain - related brain areas in mice

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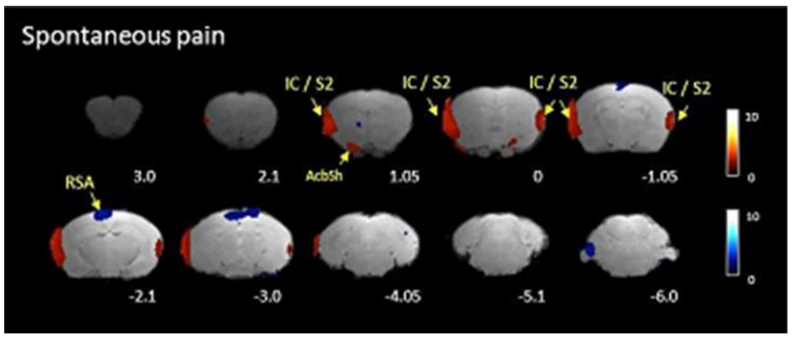
Abstract
Metastatic cancer-induced bone pain (CIBP) is a common pain in patients with advanced cancer. When cancer metastasizes to the bone, it can cause persistent and unbearable pain which reduces the patient's quality of life. Previous studies suggest that CIBP may contain neuropathic pain and nociceptive pain, but the mechanism is not well understood. In this study, positron emission tomography-computed tomography (PET/CT) imaging was used to investigate the brain changes in the CIBP mice. We inject 4T1 mouse breast cancer cells into the left femur bone marrow cavity of the BALB/c mice. Mice in control group were injected with phosphate buffered saline. The growth of the cancer in the femur bone was documented with IVIS imaging *in vivo* and histologically *ex vivo*. Breast cancer cells induced bone lysis was documented with CT scan and $Na^{18}F$-PET scan. We tested spontaneous pain behaviors with limb use observation, and mechanical and cold stimuli-induced allodynia behaviors with von Frey filaments test and acetone stimulus, respectively, on the day before bone surgery and 7-day, 10-day and 14-day after the surgery. Behaviorally, CIBP mice showed significant more pain-related behaviors 7 days after surgery. To find the related brain changes, each mouse was scanned twice, using ^{18}F-fluorodeoxyglucose (FDG) as the tracer, the first time before bone surgery and the second time 14 days after. Brain glucose metabolic activity was significantly increased in contralateral insula and bilateral primary somatosensory cortex (S1), primary motor cortex (M1), secondary motor cortex (M2), and hypothalamus; and significantly decreased in anterior cingulate cortex (ACC), nucleus accumbens (NAc), striatum, ventral posterior nucleus (VP), periaqueductal gray (PAG) in CIBP mice. Our data suggest that several brain regions in the pain matrix are involved in the cancer-induced bone pain.



Spontaneous pain related brain areas in cancer induced bone pain mice. Top left is the rostral-most and lower right is the caudal-most coronal section of the mice brain. Numerals are anterior-posterior coordinates related to the bregma (0). Red rainbow colored areas were significantly correlated with spontaneous pain score (n = 43, SPM multiple regression). These areas include bilateral insular cortex (IC) and secondary somatosensory cortex (S2), and ipsilateral shell region of the nucleus accumbens (AcbSh).

Lecture 16

Biomedical Molecular Imaging in Tissue Engineering Research

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Abstract

Tissue engineering is using appropriate porous scaffold templates based on biomaterials that can guide functional cells into desired tissues which represent the most potentially feasible strategy for attaining therapeutic purposes of different diseases. The adequate design, synthesis and processing of biomaterials into scaffolds are the keys to be success in the research and development of tissue engineering. During the development of scaffolds, many image instruments and techniques are used to do the characterization of materials, observing the growth of cells and tissues. Instruments such as magnetic nuclear resonance spectroscopy, infrared spectroscopy are used for the identification of chemical and molecular structure of biomaterials. Optical microscopy, electron microscopy, atomic force microscopy, X-ray diffraction and scattering spectroscopy are used to study morphology of materials, cells and tissues. In this talk I will use examples to discuss how these image studies are implemented in the tissue engineering research.

Lecture 17

Non-invasive transpalpebral electrical stimulation improves retinal function in mice with photoreceptor degeneration

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Abstract

Photoreceptor degeneration is one of the leading causes of blindness in developed countries.[1] In the US, approximately 1 in 3,000 individuals become blind[2] due to photoreceptor degeneration. This may be a result of gene mutations in photoreceptors, such as retinitis pigmentosa (RP), or a secondary event of retinal pigment epithelial (RPE) cell dysfunction, such as that occurred in age-related macular degeneration (AMD). To date, there is no cure for these diseases. Finding ways to attenuate photoreceptor degeneration may present a novel effective treatment for preventing vision loss in these patients. In this study, we examined the effect of a non-invasive approach of transpalpebral electrical stimulation (ES) on photoreceptor degeneration. Rhodopsin knockout ($Rho^{-/-}$) mice is a well-accepted model of retinitis pigmentosa. Transpalpebral ES was applied to 6 week old $Rho^{-/-}$ mice on one eye and the sham treatment on the contralateral eye, for 7 consecutive days; the session of ES was repeated every other week. Our data showed that daily application of ES improved retinal function in $Rho^{-/-}$ mice, as assessed by electroretinogram. Moreover, we observed reduced number of apoptotic cells and increasing number of photoreceptor cells or thickness of outer nuclear layer (where photoreceptor cells reside) in ES-treated eye compared to the sham controls in $Rho^{-/-}$ mice. Our data suggests that transpalpebral ES is safe and sufficient for halting photoreceptor degeneration. The non-invasive nature of the approach would make it an attractive approach for treating photoreceptor degeneration.

Reference:

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Lecture 18

Neurodifferentiation of Dental Pulps Stem Cells

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Abstract

Objectives

The purposes of this study were to compare the nerodifferentiation potentials of dental pulp stem cells, stem cells from human exfoliated deciduous teeth and stem cells from apical papilla.

Materials and Methods

Flowcytometry analysis of isolated dental pulp stem cells from permanent teeth (DPSCs), human exfoliated deciduous teeth (SHED and stem cells from apical papilla (SCAP) was performed for characterization of the stem cells with expression of STRO-1, CD146 and CD34. The characteristic of stem cells with neruodifferentiation was identified by using immunofluorences with neuron specific marker including nestin, beta III botulin, Fox-3, NFM. For comparison of the neurodifferentiation potential, genes expression of neuromarkers were investigated with RT-PCR analysis.

Results

The results indicated that SHED, SCAP and DPSCs were with the expression of Nestin and beta-III tublin. The RT-PCR analysis also demonstrated the increase of NMF in all cells after neural induction. It was also found that the neurodifferentiation potential of SCAP is higher than that of SHED. The DPSCs were with neurodifferentiation potential and the cells are easy to be obtained from impacted third molars. The DPSCs are available for further study and application of neural regeneration.

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Lecture 19

Organic Conductive Biomaterials for Neural Engineering

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Abstract

Interfacing materials with cells through specific ligand/receptor interactions, matching mechanical properties, and matching nanostructures are very critical in biomedical technologies. Recently, conducting polymers have emerged for various related applications, ranging from biosensing to medical bionics. Many features of conducting polymers, including simplicity for nanostructure fabrication, tailored functional groups for bioconjugation, intrinsic electrical conductivity, and soft mechanical properties, provide advantages as biomaterials for cell-related diagnostic and therapeutic platforms as well as cell engineering. These features are especially valuably for electro-active cells, such as neurons. Herein, I would like to discuss our recent efforts on designing functionalized poly(3,4-ethylenedioxythiophenes) (PEDOTs), which could specifically interact with neuron cells and provide electrical stimulation for enhanced growth and stimulated release of these cells. We developed a series of biomimetic conducting polymers based on EDOT with zwitterionic and cell targeting groups, which allows us to specifically interact with PC12 cells without non-specific adsorption of proteins. The introduction of stimuli-responsive bio-conjugation linkage enables a stimuli-responsive platform. The function of controlled cell attachment/release could be used for building noninvasively removable bioelectronics or for tissue engineering applications. Besides, the polymers displayed low impedance at low frequency range, which is ideal for providing electrical communication and stimulation on attached cells. As a result, the controlled cell attachment/release function and electrical communication with cells are achieved cooperatively from our biomimetic PEDOTs. Furthermore, together with lithography technology, the cell-substrate interaction could be spatially resolved on conducting polymers to define cell behaviors at a single cell level. The functionalized PEDOTs could be assembled into various nano/micro-morphology by fine-tuning electrochemical polymerization.

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Lecture 20

Resolving Sub-molecular Structure by Scanning Probe Microscopy

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Abstract
Scanning probe microscopy (SPM) conveys surface information at nanometer spatial resolution by raster scanning a sharp probe across the surface while maintaining a constant interaction between sthe probe and surface. This constant interaction is maintained by a sophisticated feedback loop. SPM has been extensively used to image virtually all kinds of surface structures and single molecules since it was invented more than two decades ago[1] due to its unique capability of achieving nanometer spatial resolution in ambient environment or even in liquid, unlike scanning electron microscope, where high vacuum and sample preparation are required. SPM has been used as a routine characterization instrument for supramolecule studies, including DNA assembly, DNA-protein interaction, DNA-drug interaction, lipid bilayer structures and its interaction with other molecules. Despite its unique merits, SPM is comparatively less popular compared to other microscopic techniques, like electron microscope and optical microscope in research labs. This is because SPM has a higher demand on operation expertise and the lateral resolution is limited by the finite probe size; although its vertical resolution can easily achieve a fraction of nanometer.
With the aim to further improve lateral resolution and lower the demand on operation expertise, we developed peak force tapping technology [2]. Peak force tapping technology is based on direct control over the interaction force between the probe and sample surface. This technology allows the feedback loop to be optimized fully automatically, making the measurement results independent of operator expertise. The superior force control at Pico Newton achieved by this technology enables super high resolution. This is because better force control protects sharp probes and fine features on sample surface from being damaged or deformed. By further optimizing the mechanical structure of the SPM platform, minimal thermal drift and ultra-low noise were achieved.
In this article, we will also discuss several application examples carried on the new SPM platform, including observing atomic defects on different crystals, such as mica and calcite, DNA double helix under different liquid environments, sub-molecular structures of some proteins. Two dimensional materials are hot research topics today. We used this newly developed platform to study structure and electric/electronic properties Graphene and Boron Nitride. All these results demonstrate unprecedented resolution can be achieved without any demand on operation expertise.

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Lecture 21

Computational Imaging for Molecular Characterization and Radiomics at the University of Chicago

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Abstract

The investigation of disease states requires both sensitive image acquisition systems and quantitative extraction of tumor data (radiomics). –Recent developments in PET/MRI and optical imaging have yielded novel methods of integrating instrumentation and software resulting in rapid electronics for improved imaging. —In addition, computer-extracted tumor characteristics from CAD (computer-aided diagnosis) algorithms have yielded methods for quantitative radiomics, i.e., the high throughput conversion of image data to minable data. –Quantitative radiomics has been developed to relate dynamic-contrast-enhanced magnetic resonance imaging (DCE-MRI)-based breast cancer characteristics to histopathology and genomics of the cancer tumor, demonstrating the role of tumor size, shape, and enhancement texture in prognosis and assessing risk of recurrence. It should be noted that design improvement in acquisition systems, tomographic reconstruction algorithms, and computerized interpretation methods play important roles in the future of precision medicine.

Lecture 22

Exploring Biological Specimens with Focused Ion Beam

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Abstract

Purpose: The previous attempts to employ focused ion beam (FIB) and accompanied scanning electron microscope (SEM) to mill and view biological specimens all resulted in poor image according to the literatures, though FIB has been widely used in semiconductor field. To overcome the obstacles and transform FIB to a useful biological tool, we invented some novel approaches. **Methods:** We fabricated a unique holding substrate through microprocessing such as e-beam lithography and PECVD. We utilized cultured retinal pigment epithelium cells (ARPE-19) and chloroplasts as the milling targets. They were pre-fixed with glutaraldehyde and stained with OsO_4. Then the specimens were vacuum-dried separately; neither plastic embedding nor cryo-preparation was performed. The specimens were subsequently milled by gallium ion with a FEI nova-600i FIB/SEM in different parameters. Furthermore, APRE-19 cells were treated with hydrogen peroxide or UV, and investigated. Rat retina slice sections were fixed, stained, and milled. **Results:** The ultrafine structure of ARPE-19 cells and chloroplasts could be disclosed in detail. The acquired SEM image resolution approximated TEM (Fig). Mitochondria damage and nuclear segmentation of APRE from hydrogen peroxide or UV could be observed. Tissue section of retina showed subcellular structures.

Conclusions: Under direct visualization, the FIB/SEM dual system could mill and view cell and tissue section, and the image resolution approximated TEM.

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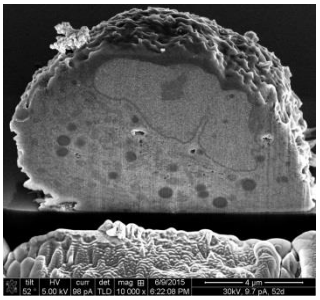

Fig. 1. ARPE-19 ultrafine structure by FIB/SEM milling/viewing.

Lecture 23

The Framework of Pulmonary Image Registration Using Chest CT for Evaluation of Radiation-Induced Lung Disease (RILD)

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Abstract

In this study a longitudinal registration algorithm is proposed for evaluating the lung parenchyma change after radiotherapy and the correlation to the given radiation strength and distribution of dosage. Treatment for patients with middle-stage and late-stage lung cancer may involve chemotherapy, radiotherapy, or a concurrent chemoradiation therapy. Radiation-induced lung damage (RILD) is a severe complication of radiotherapy in lung cancer patients that presents as a progressive pulmonary injury affecting prognosis and quality of life in patients. The proposed registration algorithm overcomes the large parenchyma change which makes the registration much harder by using anatomical structures around the lung, including using spine for the reference set of rigid registration step; using three anatomical structures: bone structures surface, including sternal, rib and spine, airway wall and surface of lower lung to describe the longitudinal difference of breath holding degree. The proposed framework includes anatomical structures extraction (airway, lobe and bone), rigid registration using spine and non-rigid registration using sampling points from the segmented components. As the first step of the proposed framework, image segmentation is a challenging task when encountering the structural abnormalities induced by the radiation. Non-rigid registration for post-treatment image is also a challenging task for achieving global optimal solution. Reference points are sampled using structural centerline and Growing Neural Gas algorithm from these anatomical feature structures for the further step of point set registration. Iterative Closet Point (ICP) is used for rigid registration whereas Coherent Point Drift (CPD) is for the non-rigid registration. Registered by the proposed longitudinal registration framework developed in this study, the correlation of regional dose distribution with longitudinal parenchyma change has been evaluated and obvious parenchyma change in the region of radiation dosage above 22 Gy and in 3~7 month is observed.

Abstracts for Poster Presentation

#1

Capture-and-release strategy for single-synapse imaging and flow cytometry

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Abstract

Alzheimer's disease (AD), a protein misfolding disorder of beta amyloid (Aβ) and tau, accounts for >50% of cases of senile dementia. AD is a neurodegenerative disease characterized by the loss of neurons and synapses. Loss of synapses in the neocortex and limbic system correlates strongly with cognitive impairment, more than other known pathological markers. Consequently, neuroscientists have been used enriched preparations of synaptosomes to study synapse dysfunction and its relationship with AD. Flow cytometry has been applied to the study of synaptosomes by several research groups. However, the immunostaining procedure of synaptosomes prior to flow cytometry represents a major technical obstacle.

Conventional immunostaining of synaptosomes for flow cytometry involves many sedimentation steps which lead to cumulative damage of these fragile organelles, resulting in great sample loss and staining variability. We devised a method to circumvent this issue by capturing synapses using electrostatic interaction. We modified synaptic surfaces with ethylene glycol bis(succinimidyl succinate) (EGS), a crosslinker that contains two amine-reactive NHS esters and a 12-atom spacer, which serves two important functions. EGS may crosslink two amine groups on different proteins to achieve synaptosome fixation. Alternatively, EGS may increase the net negative charge by neutralizing a single amine group on the synapse surface, and later impart a negative charge after the free NHS ester is hydrolyzed. In combination with negatively charged phospholipids and glycans already present on the plasma membrane, EGS-fixed synaptosomes thus carry high charge density.

EGS-treated synaptosomes are easily captured via electrostatic attraction over amine-derivatived glass surfaces treated with (3-aminopropyl)triethoxysilane (APTES). Surfaced-attached synaptosomes can be immunostained under gentle conditions just like fixed cells and imaged by fluorescence microscopy or super-resolution optical microscopy. Elution with citric acid releases synapse from the glass surface for flow cytometry analysis. This capture-and-release strategy enables high-throughput analysis of brain synapses with minimal tissue samples.

Modern flow cytometers have at least four channels for fluorescence detection, which can be used to detect a presynaptic marker, a postsynaptic marker, and two proteins of interest. The quantitative nature of flow cytometry measurements enables correlation analysis between two target proteins at the single-synapse level, which is far more sensitive than ELISA and mass spectrometry measurements. We will present colocalization data between Aβ and tau in synaptosomes.

#2

Super Resolution STED Microscopy with Focus Extension

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Abstract

Optical microscopy is a key tool to observe specimens in small length scales. Various microcopy techniques allow high resolution and high speed imaging of tissues over a large volume. However, the optical diffraction limit restricts the resolution. Super resolution microscopies are techniques to achieve resolution beyond diffraction limit.

One of the most important breakthrough in super resolution techniques is the stimulated emission depletion (STED) microscopy, which was awarded the Nobel Prize in Chemistry in 2014. A typical STED microscope uses a doughnut-shaped beam to deplete the fluorescence of specific regions of the sample while leaving a central focal spot active to emit fluorescence. Therefore, it sharpens the point-spread function (PSF), and achieves high resolution.

However, STED microscopy can provide only single layer scanning at one time. For simultaneous observation of tissue dynamic over a 3D volume, STED is limited by lack of fast axial scanning. There are reports suggesting the possibility of achieving 3D volume imaging by optical means. For example, moving objective with piezoelectric material, acousto-optic deflectors (AODs) and tunable acoustic gradient-index (TAG) lens are three possible solutions. However, moving objective have the limitation of scanning speed and difficulty of observing live animal. Problems of AODs are distortions in the focal spot shape and unstable dwelling with the focal spot. Therefore, we chose TAG lens with microscope objective. The function of TAG lens is to axially extend the focus by tuning the driving amplitude and frequency. It can easily be tuned up to kHz axial scanning rates to achieve an image sampling into an extended-depth. Moreover, TAG lens require low spatial stability of sample, which is desirable for *in vivo* observations.

In this study, we have combined STED microscopy with TAG lens to achieve super resolution along with fast axial scanning for 3D volume imaging. We demonstrated the feasibility of the technique with sample of gold nanoparticles. The PSF was sharpened in lateral direction and extended in axial direction simultaneously. Together these two powerful methods evolves to be a much more useful tool for fast and beyond diffraction limited imaging.

#3

Tissue Engineering for Resuscitation of Acute Optic Neuropathy

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Abstract

Diminution of vision cause severe impact on our daily lives. Since optical nerve regeneration is limited, nerve damage caused by neuropathy or injuries is usually difficult to fully recover. Although many diseases can be treated by ophthalmologic operation such as cataract surgery and corneal transplantation, the loss of optical nerve cannot regenerate by now. As a result, many research focus on how to regenerate optical nerve. There are many experiments shows that stem cells can differentiate into retinal pigment epithelium (RPE) or retinal ganglion cells (RGCs), but inject stem cells direct into body cause severe loss of stem cells. In order to solve this problem, lots of team use scaffold to mimic extracellular matrix (ECM) for stem cells to attach. In addition, some research show that chemical cues on scaffold can induce the differentiation of stem cells into specific cells.

We are using biocompatible polymeric materials and fabricating into 3D-scaffold to guide the growth of stem cells into axons. Three candidate materials are studied that include a polymer blend of polyurethane and cellulose, polypeptide such as silk and poly(glutamic acid)-co-poly(leucine). Since glutamic acid is one of chemical cues that promote signal transport between axon and dendrite, we are incorporating it into the polymer to induce stem cell differentiation and improve cell viability. Silk is a natural material which exhibits high compatibility with the cells. The cellulose in polyurethane has ordered structure that expects to guide the uniaxial cell growth into axons. We are using electro-spinning technique to fabricate nanofibers and to form 3-D scaffold which has high porosity for facilitating nutrient transport and cell proliferation.

We will present and discuss the results of *in-vitro* and *in-vivo* cell growth using these three candidate materials.

#4

Different Epileptic Brain Networks in Unilateral Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis Identified by the Whole Brain Tract-Based Automatic and Surface-based Analyses

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Introduction: Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) was regarded as a network disorder [1]. We proposed a surface-based analysis and a tract-specific analysis over the whole brain to detect, respectively, the GM and WM alterations in unilateral MTLE with HS. We hypothesized that the WM alterations due to MTLE with HS might affect the averaged cortical thickness of the connected GM regions. In addition, we assumed that left and right MTLE with HS should exhibit different epileptic networks.

Methods: The subjects consisted of 25 adults with MTLE and unilateral HS and 18 age-, sex- and handedness-matched healthy adult controls. MR scanning was performed on a 3T MRI system with a 32 channel phased-array head coil. Diffusion spectrum imaging (DSI) was acquired [2]. T1-weighted imaging was performed using a 3D MPRAGE sequence. The surface-based analysis pipeline consists of several stages: T1-weighted image registration, the B1 bias field estimation, the main body of WM estimation, the WM, GM, and pial surface estimation [3]. Whole brain tractography was reconstructed by tract-based automatic analysis (TBAA) [4]. Mann Whitney U-test was performed to investigate the difference in volume of sub-cortical regions, cortical thickness of cortical gyri, and mean generalized fractional anisotropy (GFA) of 74 WM tracts between controls and patients. **Results and conclusions:** This work demonstrated different epileptic brain networks between left and right MTLE with HS. The results of right MTLE with HS demonstrated the possible epileptic pathway: the Fornix, UF (uncinated fasciculus) and ATR (anterior thalamic radiation) may contribute to be a pathway to propagate the epileptic activity from the hippocampus to the orbito-frontal and middle frontal gyrus. In the contrast, left MTLE with HS exhibit the ipsilateral alterations in the limbic tracts and the superior temporal gyrus. The epileptic pathway in left MTLE with HS may be related to Papez circuit. Both patient groups showed the ipsilaterally impaired Fornix, implying that Fornix may play a role of output pathway of the sclerotic hippocampus. In conclusion, we successfully identified different epileptic networks in left and right MTLE with HS, and found more extensive WM and GM alterations in right MLTE with HS than in left MLTE with HS.

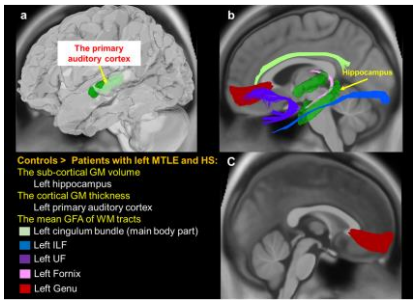

Figure. 1. Comparisons GFA of WM tracts between controls and patients with left MTLE and HS.

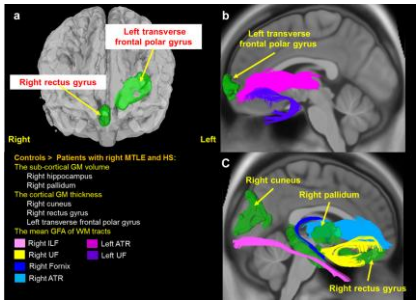

Figure. 2. Comparisons between controls and patients with right MTLE and HS.

References: [1] Engel et al. (2013) Curr. Opin. Neurol. [2] Wedeen et al. (2005) Magn Reson Med. [3] Fischl and Dale. (2000) PNAS. [4] Chen et al. (2015) HBM.

#5

Improved image segmentation of voxel-based morphometry by constructing a group-specific tissue probability map

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Abstract

For voxel-based morphometry (VBM) studies, the unified segmentation method proposed by Ashburner and Friston [1] is one of the most popular methods for estimating the tissue probability map (TPM). However, using a less representative TPM as the prior in VBM studies can either reduce the statistical power or increase the statistical bias, making the interpretation of the results more difficult. In the current study, we proposed a method to construct a group-specific TPM, and demonstrated that using this TPM as the prior can substantially improve the segmentation results. Specifically, given a set of images, our method to construct the group-specific TPM was as follow. (1) Using the unified segmentation method [1], with the SPM TPM as the prior, to estimate the TPM of each individual. (2) Rigidly aligning the estimated individual TPMs altogether according to the deformation maps estimated in (1). (3) Employing the geodesic shooting algorithm implemented in SPM [2] to iteratively estimate the mean of the (rigidly aligned) individual TPMs [3], and the mean TPM was the group-specific TPM. The above procedure was applied to the OASIS cross-sectional dataset [4] to estimate the group-specific TPM, called OAS TPM. To show the effectiveness of the proposed method, we performed an additional step (1a), where the unified segmentation algorithm was applied again to the same OASIS images to estimate the individual TPMs. Parameters of unified segmentation used in step (1a) were exactly the same as those used in step (1), except that the prior TPM of step (1a) was the OAS TPM. Fig. 1(a) displays the T_1-weighted image of an example case who presents with WM leukoaraiosis, as indicated by the white arrows. Fig. 1(b) is the GM component of this subject's TPM using the SPM TPM as the prior. It clearly shows that some of the leukoaraiosis regions are misclassified as GM. Fig. 1(c) is the results of using the OAS TPM as the prior. From this image, we can see that the misclassification is substantially reduced.

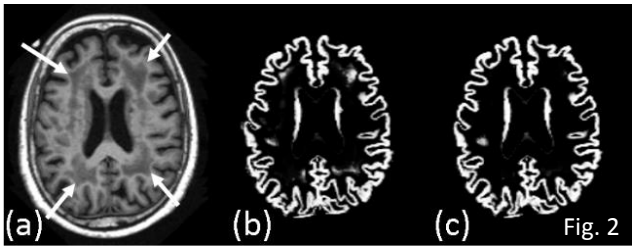

Fig. 2

Reference: [1] J. Ashburner and K. J. Friston, Neuroimage, vol. 26, pp. 839-51. [2] J. Ashburner and K. J. Friston, Neuroimage, vol. 55, pp. 954-67. [3] J. Ashburner and K. J. Friston, Neuroimage, vol. 45, pp. 333-41. [4] D. S. Marcus, T. H. Wang, J. Parker, J. G. Csernansky, J. C. Morris, and R. L. Buckner, J Cogn Neurosci, vol. 19, pp. 1498-507.

#6

Individualized prediction of ADHD based on patterns of altered tract integrity over the whole brain: a performance test on adult female with ADHD using diffusion spectrum imaging

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Abstract

Diffusion magnetic resonance imaging has been widely used to investigate structural differences between patients with mental disorders and healthy participants. However, there is no study showing the capability of individualized prediction of the mental disorder based on the differences in tract integrity over the whole brain. In this study, we used the tract-based automatic analysis (TBAA) method [1] and performed a test of the method to predict adult females with attention deficit/hyperactivity disorder (ADHD). Subjects were separated into investigating group (A) and predicting group (B). Whole-brain difference (WD) was defined from group A. A series of masks were determined at different effect sizes (ES) and cluster sizes (CS) from WD; the cluster size was defined as continuous steps with the same level of ES. Individual subjects of group B were compared step by step with WD and different indices derived from different masks were assigned to each subject to predict disease. The performance of prediction was evaluated using receiver operating characteristic (ROC) curve analysis. In this study, we selected a subgroup of ADHD, i.e. adult females with ADHD, to examine the performance of the method.

Twenty ADHD females (blue) and 20 matched healthy females (red) (ADHD: 31.3 ± 8.4, range: 18-47 years old; controls: 30.6 ± 8.1, range: 18-45 years old) were recruited in the analysis of group A. Images were acquired on a 3T MRI system with a 32-channel head coil (Tim Trio, Siemens, Erlangen, Germany). Diffusion spectrum imaging (DSI) was acquired for 102 diffusion encoding gradients with the maximum diffusion sensitivity bmax = 4000 s/mm2 using a twice-refocused balanced echo diffusion echo planar imaging sequence (TR/TE = 9600/130 ms, image matrix size = 80 x 80, spatial resolution = 2.5 x 2.5 mm2, and slice thickness = 2.5 mm). TBAA method [1] was applied to subjects to assess the whole-brain white matter properties. A total of 7400 generalized fractional anisotropy (GFA) values, named connectogram, were estimated at 7400 localized steps along 74 tracts as standardized information for each subject. WD was determined by comparing the mean GFA values at each of 7400 steps between two groups. Series of masks were determined to represent the locations containing different ES and CS in WD (ES: 0, 0.05, 0.1,…, 1; CS: 1, 2, 3,…, 15). For group B (15 ADHD: 32.1 ± 7.8, range: 19-43 years old; 17 controls: 30.1 ± 8.2, range: 18-43 years old), the whole-brain tract information of each subject was assessed by performing TBAA first. An ADHD-like index (ALI) was then estimated for each subject by using following steps. 1) ADHD-or-control maps (AOC) were estimated for all 7400 steps by comparing the connectogram with WD. Steps with GFA values closer to ADHD than to control were noted as ADHD-liked, otherwise as control-liked. 2) Masked AOC (mAOC) was derived by applying a mask to AOC. Steps passing the criteria of the mask were reserved for mAOC. 3) ALI was defined as the number of steps which were ADHD-liked in the mAOC. The performance of prediction was evaluated with ROC curve analysis by comparing the ALI scores and clinical diagnostic results.

In our findings, the highest AUC of 0.84 was found when the mask with ES > 0.75 and CS > 4 steps (about 4 mm for tract length) was applied. Our results showed that the prediction performance was high (AUC > 0.8) when we compared the steps with high ES (ES > 0.65) and more continuous neighbors along tracts (CS > 4). In conclusion, the information of the whole-brain tracts estimated by TBAA method is potentially useful for predicting adult female with ADHD. Our study warrants a prospective study to validate the diagnostic accuracy of the method.

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#7

Social communication network in high-functioning autism: a diffusion spectrum imaging (DSI) study

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Abstract

Autism spectrum disorders (ASD) are a group of neurodevelopment disorders with social communication deficit as one of the core symptoms. Among the five-level model Catani and Bambini proposed in 2014 [1], lexical / semantic processing and pragmatic integration may correspond to the symptoms of social communication deficits in high-functioning ASD [2, 3]. The anterior temporal network (inferior longitudinal fasciculus, ILF; uncinate fasciculus, UF) for lexical and semantic processing and the posterior segment of the arcuate fasciculus that linked Wernicke's area to the angular gyrus formed a temporo-parietal network (TPN) were targeted in this study. We hypothesized the alterations of the anterior temporal networks and the TPN may be related to the social communication deficits in high-functioning ASD.

Fifty-six right-handed male youths with ASD and 44 matched healthy participants were recruited in this study. All participants assessed with clinical evaluations, the intelligence test, the Chinese version of the Social Responsiveness Scale (SRS), the Chinese version of the Social Communication Questionnaire (SCQ), and MRI scans. All DSI data were acquired using a twice-refocused balanced echo diffusion echo planar imaging sequence. 102 diffusion encoding gradients with the maximum diffusion sensitivity bmax = 4000 s/mm^2 were sampled on the grid points in a half sphere of the 3D q-space. A template-based approach was employed to sample generalized fractional anisotropy (GFA) of each targeted tract. We found that youths with ASD showed reduced GFA of the right ILF and left UF as compared to TD youths. In ASD, the GFA of bilateral UF were correlated with social awareness, and the GFA of the right UF was correlated with the social communication. In TD, the GFA of the right TPN was correlated with the social communication.

The present study is the first attempt to combine DSI analysis and neuropsychological tests to investigate the associations of cores of the social communication network integrity with social communication and social awareness in youths with ASD. Reduced white matter integrity of some tracts in the social communication network was found in ASD. The correlations among SRS, SCQ and white matter integrity reveal unique characteristics in ASD. Our results indicate altered functional and structural roles of cores of the social communication network in ASD.

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#8

Group analysis of threshold-free cluster enhancement score with application to normal ageing white matter study by diffusion spectrum imaging

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Abstract

Diffusion MRI is a powerful tool to probe the microstructural integrity of the white matter. Threshold-Free Cluster Weighted Analysis (TFCW) has been developed to enhance the statistical power of clustering in the curve profiles of the white matter property. This study used template-based diffusion spectrum imaging (DSI) tractography to analyze the microstructural integrity of 74 fiber tracts over the whole brain, and applied TFCW to evaluate the age effect on the tract integrity. Table 1 shows the results of the TFCW with threshold 98%, 95%, 90% and 85%. Figure 1 displays the 4 tracts, which are the tracts with most severe degeneration.

Detailed investigation of the fiber tracts shows that the patterns of the white matter degeneration are heterogeneous. Our findings suggest that the core part of the normal ageing patterns are the bilateral fornices and the anterior part of the commissure fibers. The degeneration of the commissure and projection fibers is most pronounced in the anterior part of the brain. In conclusion, our study provides detailed degenerative patterns of the white matter tracts in normal ageing which can serve as a useful reference for neurodegenerative diseases.

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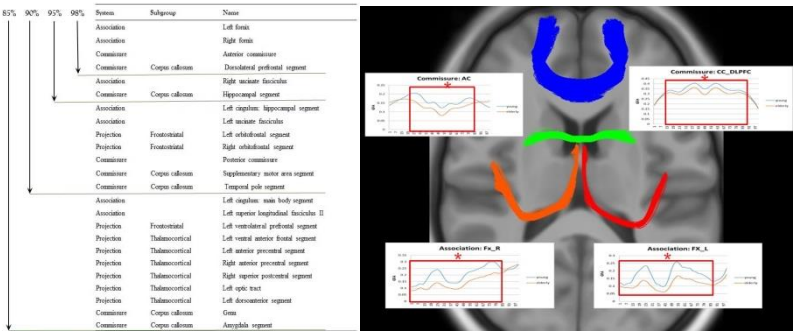

#9

Exceptional Biocompatibility of Biodegradable Polyurethane / Cellulose Fibrous Scaffold for Cardiac Tissue Engineering

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Abstract

Myocardial infarction is one of the leading causes of morbidity and mortality in human.[1] Tissue engineering has been shown as the most feasible strategy for therapeutic purposes of heart disease.[1-4] For the past two decades, efforts have been made to develop bioactive scaffolds that mimics the extracellular matrix of myocardium to regenerate and reconstruct damaged myocardium. The morphologies/structures of scaffolds need to design and control properly to guide cellular regulation and growth.

We have developed a biocompatible and biodegradable polyurethane that contains rigid segment of isophorone and soft segment of triethylene oxide polycaprolactone, terminated by urea linkage. The polymer can be electrospun into fibrous scaffold with good biocompatibility and mechanical strength. By incorporating 10 wt.% of naturally ordered ethyl cellulose into the polyurethane (PU/EC) to make scaffold, the enhanced biocompatibility and improved mechanical property are observed. The PU/EC exhibits balanced mechanical properties: high mechanical strength to support contractile cardiac tissues and good elastic flexibility to accommodate cardiac deformation. The scaffold made from aligned fibers of PU/EC exhibits interesting synergistic effects among fibers of highly ordered cellulose and elongated PU. That results in a favorable environment for enormous growth of elongated cardiac myoblast H9C2 cells. The anisotropic PU/EC scaffolds improve the cell guidance / regulation and proliferation for mimicking the extracellular matrix of myocardium. The observations imply the potential in achieving therapeutic purposes by bioengineering the developed biodegradable PU/EC scaffolds as a cardiac graft for reconstructing or regeneration damaged myocardium.

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#10

Visualization of AADC activity using 6-[^{18}F]fluoro-L-dopa (FDOPA) positron emission tomography (PET) on AADC deficiency mice under gene therapy

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Abstract

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive disease that causes defective synthesis of dopamine and serotonin, and children with AADC deficiency exhibit severe motor, behavioral and autonomic dysfunctions. We have created an IVS6+4A>T knock-in mouse model of AADC (Ddc^{KI} mice) and shown that gene therapy at the neonatal stage can rescue the phenotype. In this study, we extended the treatment to systemic therapy on young mice. After intraperitoneal injection of 7-day-old mice with either AAV9-CMV-hAADC (AAV9-AADC) or yfAAV9/3-Syn-I-mAADC (AAVN-AADC), the treated Ddc^{KI} mice showed improvements in weight gain, survival, motor function, autonomic function, and behavior, but the effects of AAVN-AADC were superior. The survival of AAVN-AADC treated Ddc^{KI} mice (95%) was slightly better than that of the AAV9-AADC treated mice (78%), but this difference was not significant. Brain AADC activity of both AAV9-AADC and AAVN-AADC treated mice was slightly elevated (2.3% and 2.7% of wild-type, respectively). 6-[^{18}F]Fluoro-L-dopa (FDOPA) PET was used to visualize the distribution of AADC activity in the mouse brain because FDOPA can be converted to dopamine and retained in the putamen. In 50-week-old AAVN-AADC-treated mice, the putamen was visualized using PET; however, no signal was observed in the untreated or AAV9-AADC-treated mice. The yfAAV9/3-Syn-I-mAADC-treated mice showed greater neuronal transduction and higher brain dopamine levels than AAV9-CMV-hAADC-treated mice, whereas AAV9-CMV-hAADC-treated mice exhibited hyperactivity. In conclusion, mice with a neurotransmitter deficiency can be rescued at a young age using systemic gene therapy, but a neuron-specific vector may be necessary.

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#11

High-resolution two-photon fluorescence microscopy with fluorescence saturation

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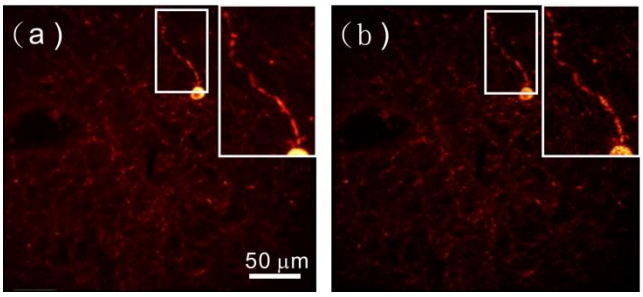
Abstract

Two-photon fluorescence microscopy (TPFM) is widely used to reveal the cell structures and molecular distribution in deep tissues. TPFM, relying on the nonlinear absorption of light wave, is capable of optically selecting an axially isolated plane of material [1] and has become a powerful tool for three-dimension fluorescence imaging. The deeper regions of thick tissue are observed, but the intensity and resolution of fluorescence are decreasing with increasing scattering and absorption [2]. Super-resolution two-photon fluorescence microscopy (*s*-TPFM), based on the fluorescence saturation effect and will be reported in this meeting, represents a revolution in the development of TPFM and is capable of improving resolution of TPFM with 1.3 times at penetration depth of 340 **μm for cerebral vasculature and neuron imaging inside a mouse brain (Fig. 1)**. The strong interaction between the fluorescence proteins and femtosecond light waves induces the saturation effect. In this condition, the fluorescence intensity is not linearly proportional to the excitation intensity and the point-spread function (PSF) is distorted, so that the PSF contains high spatial frequency components. Namely, the resolution can be improved by extracting high spatial frequency components [3]. This work is sponsored by NTU Molecular Imaging Center.



Fig~~ure~~. 1.: The Brain neurons image of (a) TPFM and (b) *s*-TPFM.

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#12

The mechanism of nonlinear scattering of gold nanospheres

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Abstract

Nonlinear phenomena provide novel light manipulation capabilities and bring numerous innovative applications, including frequency conversion, all-optical signal processing, resolution enhancement, etc. to the evolving field of plasmonics. Recently, our research group discovered a new nonlinear phenomenon on the scattering of metallic nanoparticles and applied to super-resolution microscopy that allowed spatial resolution of plasmonic nanostructures down to $\lambda/8$ [1].

Generally speaking, the origin of nonlinearities of transition metals comes from the third-order susceptibility ($\chi^{(3)}$)[2] . For example, the four-wave mixing and optical Kerr effect of gold can be described with the $\chi^{(3)}$ from hot electron and interband contributions. Another example is the saturable absorption, whose nonlinear behavior can be characterized with the $\chi^{(3)}$, or equivalently nonlinear refractive index n_2, induced form the "bleaching" of plasmonic band. However, these mechanisms are inadequate to explain nonlinear scattering in our experiments since they are typically obtained with pulsed lasers, and only consider the role of electrons, whose dynamics are on the order of picosecond or less in metallic nanostructures. In our case, the nonlinear scattering can be achieved by continuous-wave lasers. Therefore, it is highly desirable to establish a new physical model to describe the nonlinear scattering. Our idea is to include the hot lattice contribution, which was usually ignored in previous studies.

In this work, we elaborate the mechanism behind the nonlinear scattering of gold nanospheres. Based on previous experimental findings, we are aware that thermal effect should be the dominating factor for the nonlinearity. Thus, the temperature dependence of bulk gold permittivity is measured, and the corresponding variation of nanoparticle scattering is calculated. Nevertheless, the experimental variation of nanoparticle scattering is larger than 80%, while the contribution of bulk permittivity is less than 10%. We found that we had to combine the bulk permittivity change due to the hot lattice along with local field enhancement due to the nanoparticle plasmonic effects to obtain a satisfactory model for the experimental results. Our work not only opens up a new dimension for nonlinear plasmonics, but also predicts the potential of similar nonlinearity in non-plasmonic materials.

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#13

Third harmonic generation spectroscopy of free fatty acids

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Abstract

Third harmonic generation (THG) microscopy and spectroscopy was a modality suitable for *in vivo* imaging and molecular analysis, due to their characteristics of high penetration depth, high spatial resolution, with no energy deposition and photodamage [1]. Our previous study indicated that THG spectra depend on nonlinear susceptibility ($\chi 3$) distribution, which is related to the absorption characteristics of a molecule, due to resonance enhancement effects [2]. With a widely accepted analytical model used to estimate the relative susceptibility [3] and reference THG susceptibility of fused silica previous known, in this talk we show that THG spectra can be analyzed from the measured THG intensity of the sample/air interface with reference THG intensity of the fused-silica/air interface and refractive index of samples of different excitation wavelengths.

In this paper, we report THG susceptibility spectra of two free fatty acids, oleic acid (OA) and linoleic acid (LA), from the above mentioned method, where the output of an optical parametric oscillator, tunable between 1080 nm to 1500 nm, is as the THG excitation source. Our experimental results demonstrate that two types of fatty acids we used appear to have relatively higher THG susceptibility between 1240 nm to 1280 nm, differing from the strong absorbance peak around 1210 nm. Our research not only provides new spectral information for the choice of the laser excitation wavelength for future noninvasive THG imaging, but also suggests a potential method for THG microscopy and spectroscopy and molecular imaging in lipid-correlated diseases.

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#14

Non-scanning holographic light-sheet fluorescence microscopy for multi-plane imaging

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Abstract

Light-sheet based microscopic techniques offer the ability to acquire optically sectioned fluorescence images with good background rejection for tissue imaging in wide-field fashion; however, none of these techniques have the capability to image multiple fluorescent planes at the same time. We present an imaging scheme, incorporating side illumination with multiple light-sheets and multiplexed volume holographic gratings, to simultaneously obtain multi-plane images with optical sectioning capability, and no need for any axial scanning. The proposed imaging geometry is configured such that different depths inside an object are illuminated from side by multiple light sheets, and also serve as the input focal planes for subsequent multiplexed volume holographic imaging gratings. We present the design, implementation, and experimental image data demonstrating the proposed system's ability to obtain optically sectioned and multi-plane images of fluorescently labeled biological tissue samples in one shot.

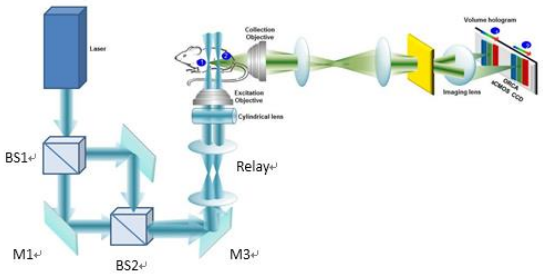

Figure 1. Schematics of experimental setup of SPIM-MVH microscope system (BS:beam splitter; M: mirror).

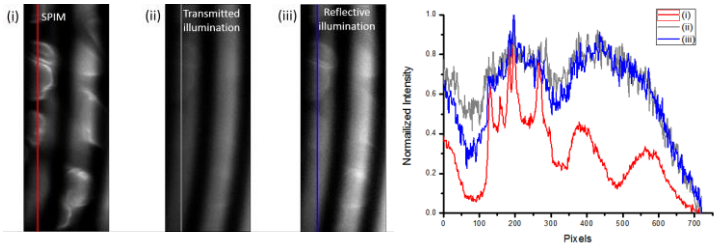

Figure 2 : (left panel) Fluorescent image of a mouse intestinal tissue sample, (i) using dual light-sheet based VHM. A(i-ii) using conventional MVH with plane-wave illumination in transmission based excitation (A(ii)),) reflection based epi-fluorescent excitation (A(iii)). (B) The profiles of Gray, blue, Red solid line and Orange dash lines in Figures A(i-iii).

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#15

Characterization of Copper Nanoparticles by Different Synthesis Methods and the Application to Photothermal Therapy

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Abstract

Copper nanoparticles have unique optical characteristics when the oxidation reaction was controlled under air, which can be stimulated by laser leading to the conversion of photon energy to heat. In the work, we developed a smooth oxidation process of Cu@polymer nanoparticles to fabricate polymer surface coating-Cu_2O shell-Cu core nanocomposite. UV-visible spectra determined the as-prepared Cu@Cu_2O@polymer nanoparticles with absorption band covered from red to near infrared (NIR) wavelengths. These nanoparticles exhibited optical and physical stability in the aqueous solution. This oxidation reaction of Cu@polymer nanoparticles was very sensitive to bromine and iodine ions. As exposure to red light, a photon-to-thermal conversion was obtained for 20-50 ppm of Cu@Cu_2O@polymer nanoparticles and 300-650 W/cm2 of laser power. Pure Cu@polymer nanoparticles plus red light did not received significant photothermal effect. In vitro studies showed no strong impact for Cu@Cu_2O@polymer nanoparticles on cell viability from 0-20 ppm and 24 h incubation compared to Cu@polymer nanoparticles. Finally, we used the Cu@Cu_2O@polymer nanoparticles to perform photothermal therapy and study the cell death pathway.

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#16

Talbot holographic illumination non-scanning fluorescence endoscopy

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Abstract

A wide-field multi-plane endoscopic system incorporating multiplexed volume holographic gratings and Talbot illumination to simultaneously acquire optically sectioned fluorescence images of tissue structures from different depths is presented. The proposed endoscopic system is configured such that several of Talbot-illumination planes occur inside a volumetric sample, and also serve as the input focal planes for the subsequent multiplex volume holographic imaging gratings. We describe the design, implementation, and experimental data demonstrating this endoscopic system's ability to obtain optically sectioned multi-plane fluorescent images of tissue samples in wide-field fashion without scanning in lateral and axial directions.

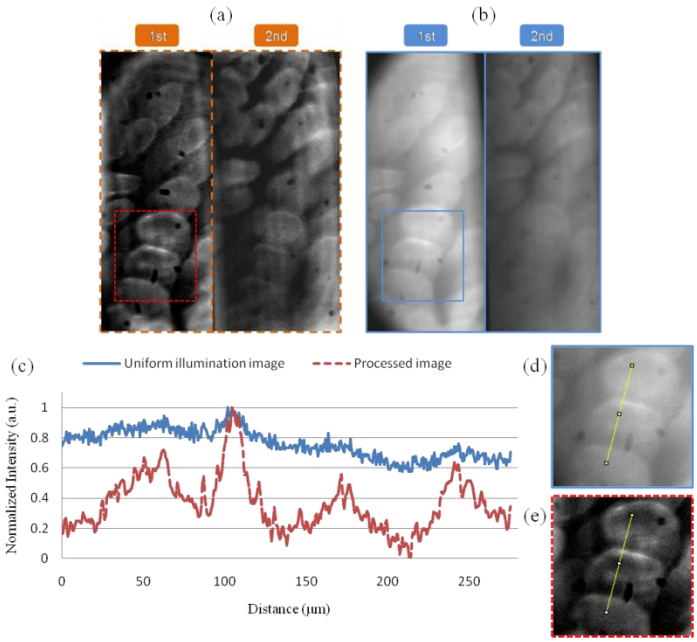

Fig.1. (a) HiLo processing image and (b) uniform illumination images of mouse intestine. 1st corresponds to depth 1 image while 2nd is the image coming from a deeper depth within a thick tissue.(c) Normalized intensity cross section plot along the yellow line shown in zoom-in image Fig.(d) and (e). The solid (blue) and dash (red) lines depict the normalized intensity profiles of uniform illumination image and processing image at the depth 1, respectively.

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#17

Hydrogel of Glycol Chitosan Combined with Gelatin for Human Adipose-Derived Stem Cells

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Abstract

The chitosan hydrogel has a nice biocompatibility and degradability so that it is applied broadly in tissue engineering. However, the chitosan gel needs something to improve the viability of cells. Therefore, the soluble glycol chitosan is combined with gelatin, which is degradable and able to make cells adhere and proliferate.

Human adipose-derived stem cells (hASCs) can be found in subcutaneous adipose tissue. They have the ability to differentiate into different lineage including osteogenic, adipogenic and chondrogenic lineage. By adhering on the hydrogel, we hope to make hASCs reserve their ability of differentiation.

The hydrogel of glycol chitosan and gelatin can be the carrier of hASCs for implanting into tissue. The degrading rate of glycol chitosan and gelatin are different, so that it is possible to make hASCs leave the hydrogel when the more gelatin degrades after a period of time. Therefore, the cells can stay in and cure the tissue.

The cellular behaviors such as differentiation and proliferation of hASCs are also different when culture on different composition of chitosan/gelatin mixture. The gene expressions of hASCs may also vary due to the difference ratio of chitosan/gelation composition. The second part of the experiments showed that the scaffold environment, even with same materials but different ratio of mixture, are able to alther the stem cell fate by examining there stem cell fate with guided differentiation and performing RT-PCR for quantitatively analysis of gene expression.

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#18

Multifunctional Nanocarriers for Imaging, Delivery and Gene Manipulation

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Abstract

The purpose of this study is to develop a serum-resistible nanocarrier for delivering therapeutic nucleic acids efficiently with imaging properties simultaneously. A newly designed guanidinium-based cholesterol was mixed with superparamagnetic iron oxide nanoparticles (SPIOs) to form GCC-Fe_3O_4 nanocarriers. To evaluate the transfection efficiency and cytotoxicity, fluorescent-labeled oligonucleotides (ODNs) were transfected as indicators. Fluorescent microscopy, confocal microscopy, and harmonic generation microscopy were used for evaluations.

Third harmonic generation (THG) has been used as a noninvasive nonlinear optical imaging tool for biological researches [1][2]. Since THG nonlinearity exists in most biomaterials, such signals can be observed among the lipid-coated iron oxide nanoparticles such as GCC-Fe_3O_4. On the other hand, SPIO has already been a FDA approval contrast agent to use in magnetic resonance imaging (MRI) for clinical diagnosis [3]. Thus, GCC-Fe_3O_4 nanocarriers can be used as image probes for tracking the outcomes of gene therapeutic manipulations.

The results indicated that GCC-Fe_3O_4 nanocarriers were highly stable and consistent in size over time. They showed great transfection efficiency as well as low cytotoxicity with or without serum conditions. Such nanocarriers not only worked well in cancer cells, but also ideal for gene manipulation in primary cells and even stem cells. With the imaging properties, we found those nucleic acids were delivered into cells together with the nanocarriers.

To conclude, we developed a biocompatible multifunctional nanocarrier for a wide variety of biomedical applications. With high gene delivery efficiency and imaging capabilities, GCC-Fe_3O_4 nanocarriers are suitable to be utilized for further noninvasive *in vivo* cell tracking and gene therapeutics.

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#19

A Fiber-Based Femtosecond Laser Source for *In Vivo* Harmonic Generation Microscopy

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Abstract

Multiphoton fluorescence microscopy and harmonic generation microscopy are well known as *in vivo* imaging technique [1] [2]. In order to achieve deeper penetration depth, it usually employs femtosecond laser sources around 1200 nm in which light-tissue interaction like photon absorption and scattering is greatly reduced [3]. Conventional solid state femtosecond laser source like Ti : sapphire laser cascaded with optical parametric oscillator or Cr : forsterite solid state laser can provide the laser is easily affected by temperature and humidity and it's not stable for medical use [4] [5].

In this article, we demonstrated a 7.5 MHz (&11.25MHz) repetition rate and 6.5 nJ pulse-energy fider-based femtosecond laser source at 1160 nm. It was achieved by a soliton self-frequency shift in photonic crystal fiber and a second harmonic generation in a quasi-phase matching nonlinear crystal. We expect that such fiber-based laser system could replace the conventional solid state laser system to increase the stability of harmonic generation microscopy in clinical research.

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#20

CREATION OF CELL-DERIVED EXTRACELLULAR MATRIX OF BOTH RANDOM AND ALIGN ECM SCAFFOLD AS A TEMPLATE FOR VASCULAR TISSUE ENGINEERING

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Abstract

Biomedical researchers found great interest in extracellular matrix (ECM) scaffolds derived from cultured cells for tissue engineering applications. ECM scaffolds can be prepared from autologous cells to generate autologous ECM (aECM) scaffolds. It can avoids the undesired host responses that may be induced by allogenic or xenogenic materials and circumvents the limited supply of autologous tissues.

In this study, we first fabricate random and align PLGA meshes as a template for cell culturing using PLGA electrospun fibres. Afterward, Human umbilical vein endothelial cells (HUVECs) and Human adipose stem cell (hASCs) were seeded onto the PLGA template. Cell-ECM-PLGA constructs were formed by the culturing cells in the PLGA mesh for five to six days. Finally, the whole product was decellularized by freeze-thaw cycling and NH4OH aqueous solution treatment to remove the undesired PLGA template. The ECM left behind will be freeze-dried and sterilized.

Finally, hASCS were seeded onto the ECM scaffold and tested *in vivo* by using Chick Chorioallantoic Membrane (CAM) assay. The results showed that the ECM scaffold provided wonderful effort in angiogenesis. And the ECM scaffold fabricated in the align PLGA mesh showed a better result compare to the random PLGA meshes.

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#21

The Influence of pSBMA Hydrogels Incorporated with RGD on the Proliferation and Adipogenic Differentiation of hASCs

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Abstract

Zwitterionic poly-sulfobetaine methacrylate (pSBMA) has been well studied for its superhydrophilic and ultralow biofouling properties, making it to be a promising material for high biocompatibility.

Adipose-tissue derived stem cells (ASCs), which are isolated from fat tissues, are easily obtainable and also can differentiate to multiple lineages, including adipogenesis, osteoblast and chondrocytes.

Although pSBMA being ultralow biofouling material, it can be modified with peptides containing the amino acid sequence arginine-glycine-aspartic acid (Arg-Gly-Asp, RGD) to promote cell adhesion ability. In this study, we are seeding human adipose-tissue derived stem cells (hASCs) on different concentration RGD-modified PSBMA to observe hASCs cell adhesion ability and adipogenic differentiation.

Keywords: sulfobetaine methacrylate, human adipose-tissue derived stem cells, adipogenic differentiation.

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#22

The applications of microfluidics in the interaction of dimensionality toward cardiac myoblast and adipose-derived stem cells differentiation ability

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Abstract

Dimensionality is a physical cue that has been discussed less frequently among the various physical cues that influence cell behaviors. In this study, we took the advantage of microfluidics to fabricate three-dimensional (3D) gelatin-based scaffolds to mimic the natural circumstances of cell growth in an organism. We further compared the differences of cellular behaviors between 2D and 3D conditions. The models used in the presented study are H9c2 rat cardiac myoblast and human adipose-derived stem cell (hASC), both of which have differentiation ability.

H9c2 is able to differentiate into skeletal or cardiac myocytes. Therefore, in this series of experiments, we aimed at investigating how dimensionality contributes to different types of muscle differentiation. We have found that H9c2 cells tended to fuse into multi-nucleated skeletal myotubes in 3D scaffold and differentiated into cardiac cells on 2D plane. However, the influence of dimensionality on cardiac differentiation was far less than that of chemical stimulation.

hASC possesses multipotent differentiation ability toward osteogenic, adipogenic, myogenic and chondrogenic lineages. Specifically, we investigated osteogenic and adipogenic differentiation capability of hASC under different dimensional conditions. According to our results, the 3D environment supported adipogenesis and the 2D condition promoted osteogenesis. Our future work will focus on finding the factors which influence differentiation capability on the matrixes in different dimensionality. Furthermore, the myogenesis and chodrogenesis will also be investigated.

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#23

All-in-focus whole-brain microscopy for functional analysis

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Abstract

Brain functions rely on numerous activities among thousands of neurons. Spatially, the size of a cell body is several micrometers, but the length of fibers span millimeters to meters in three dimensions. Temporally, neural dynamics typically occur within few milliseconds. Therefore, an ideal brain research method should exhibit following features: (1) noninvasiveness; (2) micrometer spatial resolution; (3) deep tissue penetration; (4) millisecond temporal resolution; and (5) large field of view to cover a whole brain. Two-photon microscopy automatically fulfills (1)-(3), while 3D point or line scan techniques [1, 2] satisfy (4). Light-field [3] and light sheet microscopy [4] can meet (5). However, 3D point or line scan requires very high sample stability, which is difficult for living tissue. Light-field microscopy lacks deep penetration due to its one-photon nature, and light sheet microscopy is only applicable to transparent tissue. Here, we report a novel all-in-focus imaging method that not only meets all the requests, but also is compatible with a commercial two-photon microscope. With live adult *Drosophila*, whose brains are highly scattering, our technique provides noninvasive observation of whole-brain neural signal flow on the basis of individual neuron and millisecond resolutions. Our work paves the way toward functional connectomes and will serve as a platform for future brain studies.

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#24

The proliferation and differentiation of porcine adipose-derived stem cells by keratins incorporated with chitosan-Az

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Abstract

Keratin is a biodegradable material with good biocompatibility and intrinsic bioactivity. In this study, we fabricated a keratin-based biomaterial with the addition of chitosan-Az and find out if it can achieve a positive effect in bone tissue engineering.

We extracted keratins from human hair, and then we added in chitosan-Az which had been modified by photochemical in advanced to enhance the mechanical properties of keratins. We used this keratin-based material to fabricate films and scaffolds and cultured cells on them separately.

Our research clearly shows keratin is a material that has outstanding bioactivity and biocompatibility. With significant evidence, we show that keratin is beneficial to cell adhesion, cell proliferation and cell differentiation.

Keywords: keratin, chitosan-Az, cell differentiation.

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#25

Data Driven 3D high-resolution structured illumination fluorescent microscopy based on Bayesian estimation

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Abstract

Light induced fluorescent microscopy has long been developed to observe and understand the object at microscale, such as cellular sample. However, the transfer function of lens-based imaging system limits the resolution so that the fine and detailed structure of sample cannot be identified clearly. The techniques of resolution enhancement are fascinated to break the limit of resolution for objective given. In the past decades, the resolution enhancement imaging has been investigated through a variety of strategies, including photoactivated localization microscopy (PALM), stochastic optical reconstruction microscopy (STORM), stimulated emission depletion (STED), and structure illuminated microscopy (SIM) [1]. In those methods, only SIM can intrinsically improve the resolution limit for a system without taking the structure properties of object into account. In this paper, we develop a SIM-based system associated with Bayesian estimation [2], furthermore, with optical sectioning capability rendered from HiLo processing [3], resulting in high resolution through 3D volume. Our proposed 3D microscopic imaging can provide optical sectioning with resolution enhanced performance, and be robust to noise owing to the Data driven Bayesian estimation reconstruction. For validating the 3D SIM, we show our simulation result of algorithm, and the experimental result demonstrating the 3D resolution enhancement.

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#26

Fast wide-field optical sectioning microscopy with structured illumination for 3D tissue imaging

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Abstract

A wide-field microscopy system incorporating structured illumination and tunable lens for fast axial scanning to obtain 3D imaging is presented. The proposed microscopic system is configured such that the periodic gird pattern illuminated on objective plane for structured illumination, while a tunable lens on Fourier plane is able to obtain optically sectioned images from tissue samples without mechanical scanning. We describe the design, implementation, and experimental data demonstrating this proposed microscopic system's ability to obtain optically sectioned 3D fluorescent images of biologic samples such as nervous systems in high-speed and high-resolution fashion.

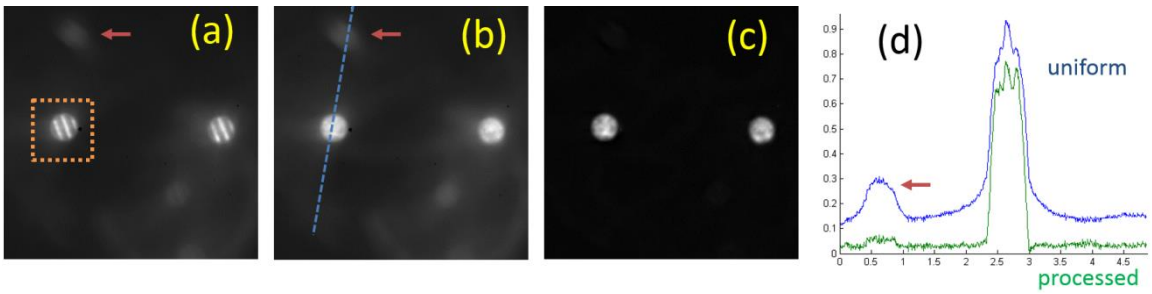

Fig.1. (a) Structured illumination of 10um fluorescence beads with 278 lp/mm grid pattern in object place(yellow dashed window) and out out-of-focus bead without grid pattern(red arrow). (b) uniform illumination without grating pattern. (c) processed resultant images –from (a) and (b) with suppressed out-of-focus background . –(d) contrast line(blue dashed line of (b)) of uniform illumination (blue line) and processed image (green line). The out-of-focus image, –pointed by red arrow, is suppressed.

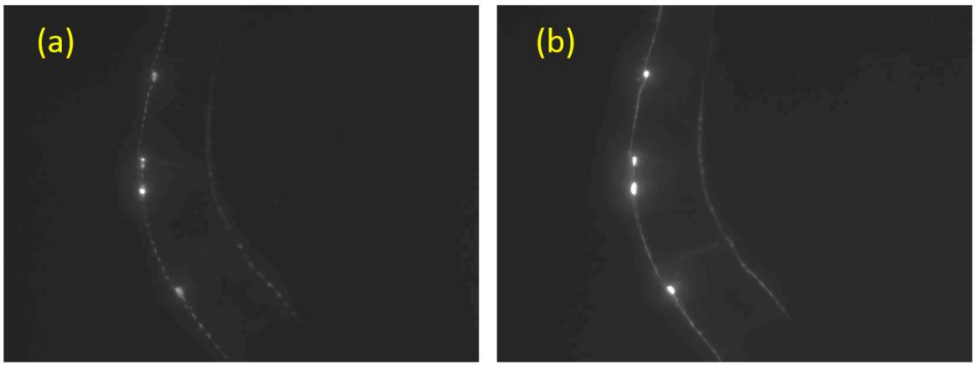

Fig.2. Fluorescence image of a nematode worm's nervous system with (a) structured illumination and (b) standard uniform illumination.

#27

Incoherent digital volume holographic microscopy for 3D imaging

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Abstract

Digital holographic microscopy (DMH) has great potentials for a variety of biomedical applications. The key advantage is that the sample does not require vertical optical axis scanning but uses computational reconstruction to get in-focus three-dimensional images. However, DHM, in general, requires the formation of a hologram using stringent coherent condition, and thus it can not obtain 3D images under incoherent sources, such as white light or emitted fluorescent light. The early studies such as Fresnel incoherence correlation holography [1] and incoherent digital holographic adaptive optics [2] have crossed this barrier by using incoherent light in holography. While the former requires expensive spatial light modulators with limited pixel resolution while the later needs mechanical scanning to match short optical path length.

In this article, a self-interference 4-f imaging system with two multiplexed volume holographic pupils is proposed. The diffracted signal beam of the sample from a volume holographic pupil will interfere with its corresponding common-path reference beam from the other one; therefore, self interfered patterns will be produced and recorded at the CCD plane. An air-force resolution target was used in our proof-of-concept imaging system. Fresnel propagation method can then be utilized for digital reconstruction. Fig 1(a) and (b) show the raw data captured by the CCD. Fig 1(c) and (d) are the reconstructed images. The image with two multiplexed volume holographic pupils is successfully reconstructed with significantly enhanced contrast (Fig. 1(d)) under incoherent light source.

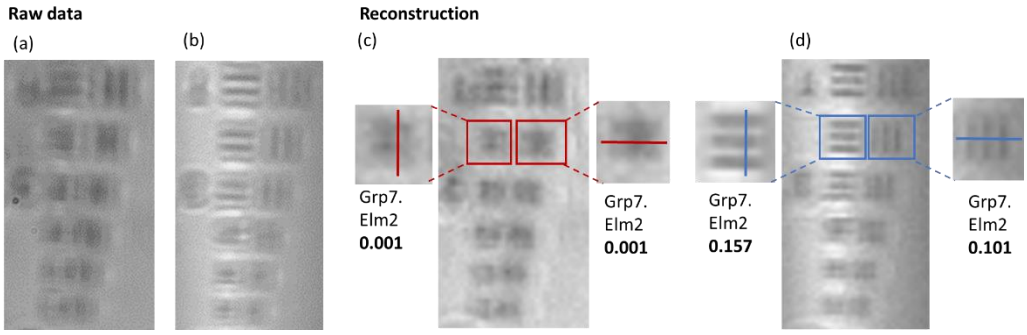

Fig 1. Raw data in (a) zero order (b) first order, reconstruction in (c) zero order (d) first order.

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#28

High photo-stability, low saturation intensity organic light emitting device dye used in stimulated emission depletion microscopy

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Abstract

Optical microscopy has long been used in biomedical research because of its easy operation and non-invasive feature. However, resolution of optical microscopy is limited to roughly half of the wavelength. To overcome the limit, several methods such as photo-activated localization microscopy (PALM) and stimulated emission depletion (STED) microscopy have been demonstrated, and received Nobel Prize of Chemistry last year. Compared to localization microcopy, STED exhibits much higher imaging speed. The principle of STED is to sharpen the point-spread-function by overlapping excitation beam with a doughnut-shaped depletion beam to turn-off the peripheral fluorescence signal. Nonetheless, it typically requires exceptionally strong depletion intensify, which usually causes photo-toxicity and photo-bleaching, and thus hinders the application of STED microscopy. To solve these issues, it is vital to find a suitable dye that not only requires low depletion intensity, but also exhibits outstanding photo-stability.

In this report, we combine STED with Spiro-BTA, which is an organic light emitting device (OLED) dye. The reasons to adopt an OLED dye are because it is very bright, stable, and with large cross-section, which shares the same features with an ideal STED dye. In addition, Spiro-BTA is bio-compatible and non-blinking [1, 2]. Experimentally, we measure the fluorescence signal intensity versus depletion intensity and find that intensity to deplete 50% fluorescence is lower compared to most commonly used STED dyes. After 5-minute exposure and repeatedly switching the fluorescence on/off, no photo-bleaching is observed, manifesting the excellent photo-stability of the OLED dye. With the confirmed STED properties of Spiro-BTA, we load it into 50-nm silica nanospheres and further verify that the resolution is enhanced at least two folds. Our results not only point out a new direction when searching for suitable STED dyes, but also provide an interesting example of combining OLED and STED, which are both at the frontiers of research.

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#29

TBZ Derivatives as Potential PET Imaging Agent for Vesicular Monoamine Transporters

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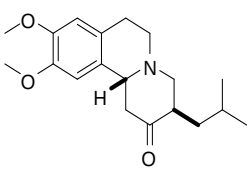
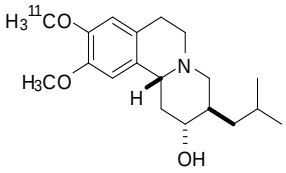
Abstract

In August 2008, racemic tetrabenazine (3-(2-methylpropyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[ ]quinolizin-2-one, (±)-TBZ) was approved for the treatment of chorea associated with Huntington's disease in USA. The primary pharmacological action of TBZ and its active metabolites, such as dihydrotetrabenazine (DTBZ), is to deplete the levels of monoamines within the central nervous system by inhibiting the human vesicular monoamine transporter 2 (VMAT2). Therefore, radiotracers derived from TBZ can be potential biomarkers of VMAT2 for positron emission tomography (PET) imaging. Here, we radiosynthesized 10-(+)-^{11}C-DTBZ, and evaluated its potential as a VMAT2 radioligand. The microPET scan work are still in progress and the result will be compare with 9-(+)-^{11}C-DTBZ. Derivative TBZ labeled with ^{18}F ($T_{1/2}$ = 110 min) instead of ^{11}C ($T_{1/2}$ = 20 min) would improve their utility and availability for imaging VMAT2 in clinical settings. (2*R*, 3*R*, 11b*R*)-9-Fluoropropyl-(+)-dihydrotetrabenazine (FP-(+)-DTBZ) was found to have nanomolar binding affinity to VMAT2 (K_d = 6.76 nM) and could differentiate normal controls from Parkinson's disease subjects. Here, we report the preparation of ^{11}C and ^{18}F-labelled TBZ derivative and PET study using male Sprague-Dawley rats with ^{11}C and ^{18}F-labelled TBZ derivative. Further studies of these compounds as potential imaging agents for VMAT2 are currently in progress.



TBZ



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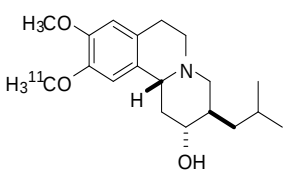

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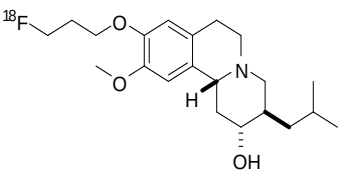

^{18}F-FP-(±)-DTBZ

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