



5th Taiwan-Japan

Academic Research Organization Workshop

PROGRAM & ABSTRACTS

September 26, 2019

Tohoku University, Sendai, Japan





Sep. 25-27, 2019

5th Taiwan-Japan Academic Research Organization Workshop Agenda

Theme : Big data and cancer translational research

Date : Sep.26, 2019

Venue : Tohoku University, Sendai, Japan

星陵 Auditorium (morning)

良陵会館(afternoon)

Sponsored and Organized : ARO Council (Japan), TSPA(Taiwan),

Cosponsored: National Cancer Center Hospital (Japan)

Sep.25, 2019

Arrival / No activity

Sep. 26, 2019:

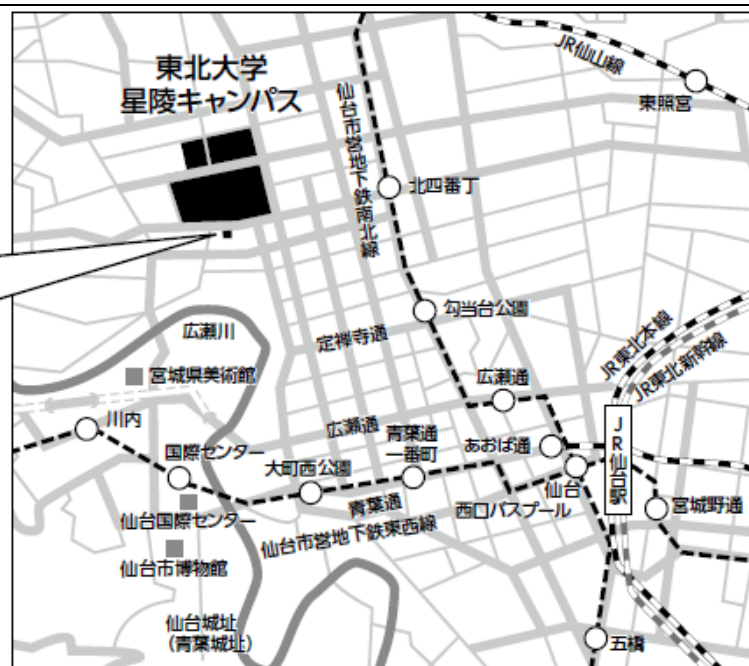
08:00-16:10 Workshop

19:00-21:00 Banquet: Local Diner & Terrace Bar VALNICO

<https://akr8035105790.owst.jp/en/>

Sep.27, 2019

Departure



Sep. 26, 2019	
Big data and Cancer Translational Research	
Time	Program
08:00-08:30	Registration
08:30-08:40	Opening Remarks Norihiro Sato(佐藤典宏), Hokkaido University Pan-Chyr Yang (楊泮池), National Taiwan University
Session I: Biobank and Big Data (12 min lecture +3 min Q&A/each speaker+10 min discussion) (星陵 Auditorium)	
Moderator	(JP) Atsushi Ohtsu (大津敦), National Cancer Center Hospital East (TW)Yi-Hsin Connie Yang (楊奕馨), National Health Research Institutes
8:40-8:55	Genome-omics analyses in Tohoku Medical Megabank project toward the realization of personalized medicine Kengo Kinoshita (木下 賢吾), Tohoku University
8:55-9:10	Digital Medicine and Precision Health Management Ueng-Cheng Yang (楊永正), National Yang-Ming University
9:10-9:20	Discussion
Moderator	(JP) Kengo Kinoshita (木下 賢吾), Tohoku University (TW)Yi-Hsin Connie Yang (楊奕馨), National Health Research Institutes
9:20-9:35	A Nation-Wide Genome Screening Platform for New Agent Developments (SCRUM-Japan) Atsushi Ohtsu (大津敦), National Cancer Center Hospital East
9:35-9:50	Big Data Analysis for Cancer and Rare Disease Shih-Feng Tsai (蔡世峯), National Health Research Institutes
9:50-10:00	Discussion
Moderator	(JP) Kengo Kinoshita (木下 賢吾), Tohoku University (TW)Yi-Hsin Connie Yang (楊奕馨), National Health Research Institutes
10:00-10:15	Kobe Project for the Exploitation of Newer Strategies to Reduce Social Burden of Dementia Yoji Nagai(永井 洋士), Kobe University
10:15-10:30	An AI Perspective on Individualized Cancer Risk Yu-Chuan Jack Li (李友專), Taipei Medical University
10:30-10:40	Discussion
10:40-11:00	Break
Session II: Big data (12 min lecture+3min Q&A/each speaker+10 min discussion/pair)	
Moderator	(JP) Yoji Nagai(永井 洋士), Kobe University (TW) Ueng-Cheng Yang (楊永正), National Yang-Ming University
11:00-11:15	Risk factors of dementia in subjects with cerebral vascular disease based on big

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Agenda

	data Bin Zhou(周玢), TRI
11:15-11:30	A Stroke Data Repository to Facilitate Big Data Research: A Taiwan and NIH Collaborative Experience Yang C. Fann (范揚政), National Institutes of Health
11:30-11:40	Discussion
Moderator	(JP) Yoji Nagai (永井 洋士), Kobe University (TW) Ueng-Cheng Yang (楊永正), National Yang-Ming University
11:40-11:55	Beyond Multicenter Trial Results: Application of Big Health Databases to Establish Real-world Evidence Chung Y. Hsu (許重義), China Medical University
11:55-12:10	Impacts of space and global environmental factors on human health Tsutomu Nishimura(西村 勉), Kyoto University
12:10-12:20	Discussion
12:20-13:30	Lunch break
Session III : Special Session for Cancer Translational Research (25 min lecture +5 min Q&A/each speaker) (艮陵会館)	
Moderator	Norihiro Sato(佐藤典宏), Hokkaido University
13:30-14:00	Oncolytic virus therapy in Patients with Castration-Resistant Prostate Cancer Hiroshi Fukuhara (福原浩), Kyorin University(杏林大学泌尿器科)
Session IV : Cancer Translational Research(12 min lecture + 3 min Q&A/each speaker+10 min discussion)	
Moderator	(JP) Toshiro Nishida (西田 俊朗), Japan national cancer center hospital (TW) Andrew H.-J. Wang (王惠鈞), Academia Sinica
14:00-14:15	International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX Study) Hideki Ueno (上野 秀樹), National Defense Medical College
14:15-14:30	Long-Term Oncologic Results of Laparoscopic D3 Lymphadenectomy with Complete Mesocolic Excision for Right-Sided Colon Cancer with Clinically Positive Lymph Nodes Jin-Tung Liang (梁金銅), National Taiwan University Tzu-Chun Chen(陳姿君), National Taiwan University
14:30-14:40	Discussion
Moderator	(JP) Toshiro Nishida (西田 俊朗) , Japan national cancer center hospital (TW) Andrew H.-J. Wang (王惠鈞), Academia Sinica
14:40-14:55	AI for Breast Cancer Diagnosis study Masahiro Takada (高田正泰), Kyoto University
14:55-15:10	Radiotherapy versus low-dose tamoxifen following breast conserving surgery for low-risk and estrogen receptor-positive ductal carcinoma in situ of breast: an international open-label randomized non-inferiority trial (TBCC and Japan ARO-DCIS trial)

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Agenda

	Sung-Hsin Kuo (郭頌鑫), National Taiwan University
15:10-15:20	Discussion
Moderator	(JP) Hiroshi Fukuhara (福原浩), Kyorin University (TW) Andrew H.-J. Wang (王惠鈞), Academia Sinica
15:20-15:35	Rare Cancer Registry and ReGISTry NETwork in Asia Toshirou Nishida (西田 俊朗), Japan national cancer center hospital
15:35-15:50	Testing the Hypothesis of Reducing Cancer Risk with GSK-3 Inhibitor Using Taiwan National Health Insurance Database Yi-Hsin Connie Yang (楊奕馨), National Health Research Institutes
15:50-16:00	Discussion
16:00-16:10	Closing Remarks Akira Myoui (名井陽), Osaka University Andrew H.-J. Wang (王惠鈞), Academia Sinica

Sep.26, 2019

Time	Banquet (Local Diner & Terrace Bar VALNICO)
19:00-19:10	Norihiro Sato(佐藤典宏), Hokkaido University
20:50-21:00	Andrew H.-J. Wang (王惠鈞), Academia Sinica

Preface

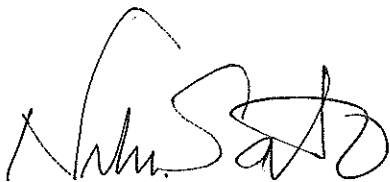
September 2019

Dear Colleagues,

Welcome to 5th Taiwan-Japan Academic Research Organization Workshop, held on September 26, 2019, at Tohoku University. On behalf of the organizing committee, that is Japan Academic Research Organization council and Translational Innovation of Biopharmaceutical Development-Technology Supporting Platform Axis (TSPA), I would like to express my warm welcome to all participants.

We have established collaborative relationships between Japan and Taiwan ARO over the past four years with focus on our activities from ARO itself to the translational research of cancer and rare diseases. In this workshop, our discussion will be mainly on big data and biobank, which provide new development for clinical trials and medical technologies. Through this opportunity, I believe, we can exchange our expertise and experience on cancer and rare disease innovation between Japan and Taiwan, and contribute better patient care and medical health.

Thank you for your participation and I hope a great success of our workshop.

A handwritten signature in black ink, appearing to read 'Norihiro Sato', with a stylized, cursive script.

Norihiro Sato,

Chairman of the board of Directors,

Japan ARO Council.

Professor, Director,

Clinical Research and Medical Innovation Center, Hokkaido University Hospital.

Opening Remarks

Norihiro Sato, Hokkaido University
Pan-Chyr Yang, National Taiwan University

Opening Remarks



Norihiro Sato, MD, PhD

Deputy Director, Hokkaido University Hospital (in charge of research)
Director / Professor, Clinical Research and Medical Innovation Center,
Hokkaido University Hospital
Email: nhsato@med.hokudai.ac.jp

Profile

I graduated from Hokkaido University School of Medicine in 1985, and majored in hematology/oncology. My career in the field of translational/clinical research started as Deputy Director of Translational Research and Clinical Trial Center in Hokkaido University Hospital (HUH) in 2007. Since then, I have worked in this field, and assumed a current position as Director/Professor of Clinical Research and Medical Innovation Center at HUH in 2009.

Affiliated Academic Society : Science Council of Japan (Member), ARO Council (Chairman of the board of Directors), Japan Society of Clinical Trials and Research (Trustee), Society for Regulatory Science of Medical Products (Trustee), The Japanese Society of Clinical Pharmacology and Therapeutics (Representatives, Special Advising Doctor), Society for Clinical Trials (SCT), etc.

Professional interests and specialties

1. Clinical/translational research
2. Hematology/Oncology

Selected Publications

1. Ichiro Kusumi, Yuki Arai, Ryo Okubo, Minoru Honda, Yasuhiro Matsuda, Yukihiro Matsuda, Akihiko Tochigi, Yoshiteru Takekita, Hiroyoshi Yamanaka, Keiichi Uemura, Koichi Ito, Kiyoshi Tsuchiya, Jun Yamada, Bunta Yoshimura, Nobuyuki Mitsui, Sigehiro Matsubara, Takayuki Segawa, Nobuyuki Nishi, Yasufumi Sugawara, Yuki Kako, Ikuta Shinkawa, Kaoru Shinohara, Akiko Konishi, Junichi Iga, Naoki Hashimoto, Shinsaku Inomata, Noriko Tsukamoto, Hiroto Ito, Yoichi M. Ito and Norihiro Sato : Predictive factors for hyperglycaemic progression in patients with schizophrenia or bipolar disorder. *BJPsych Open*, Nov.2018, Volume 4, Issue 6, 454-460
2. Kenji Yamada, Hideaki Shiraishi, Eishin Oki, Mika Ishige, Toshiyuki Fukao, Yusuke Hamada, Norio Sakai, Fumihiro Ochih, Asami Watanabe, Sanae Kawakami, Kazuyo Kuzume, Kenji Watanabe, Koji Sameshima, Kiyotaka Nakamagoe, Akira Tamaoka, Naoko Asahina, Saki Yokoshiki, Takashi Miyakoshi, Kota Ono, Koji Oba, Toshiyuki Isoe, Hiroshi

Opening Remarks

Hayashi, Seiji Yamaguchi, Norihiro Sato; Open-label clinical trial of bezafibrate treatment in patients with fatty acidoxidation disorders in Japan. *Molecular Genetics and Metabolism Reports*, Volume 15, June 2018.

Opening Remarks



Pan-Chyr Yang (楊泮池), MD, PhD

Professor,
Department of Internal Medicine, College of Medicine,
National Taiwan University
E-mail: pcyang@ntu.edu.tw

Education:

1990 Ph.D., Graduate Institute of Clinical Medicine, National Taiwan University
1979 M.D., College of Medicine, National Taiwan University,

Current Positions:

2006- Academician, Academia Sinica
1993- Professor, Department of Internal Medicine, National Taiwan University

Working Experiences:

2013- 2017 President, National Taiwan University
2011-2013 Superintendent, National Taiwan University Cancer Center
2007-2013 Dean, College of Medicine, National Taiwan University
2005-2007 Director, NTUH National Clinical Trial and Research Center
2003-2008 President, Taiwan Society of Pulmonary and Critical Care Medicine
1999- Fellow, Institute of Biomedical Sciences, Academia Sinica
1998-2004 Chairman, Department of Internal Medicine, National Taiwan University Hospital

Awards:

Fellow, National Academy of Inventors (NAI)	2015
Academician, The World Academy of Sciences (TWAS)	2008
Academician, Academia Sinica	2006

Recent Publications:

1. Lin CW, Wang LK, Wang SP, Chang YL, Wu YY, Chen HY, Hsiao TH, Lai WY, Lu HH, Chang YH, Yang SC, Lin MW, Chen CY, Hong TM, Yang PC: Daxx inhibits hypoxia-induced lung cancer cell metastasis by suppressing the HIF-1 α /HDAC1/Slug axis. *Nat Commun.* 2016 22;7:13867.
2. Huang KY, Kao SH, Wang WL, Chen CY, Hsiao TH, Salunke SB, Chen JJ, Su KY, Yang SC, Hong TM, Chen CS, Yang PC: Small-molecule, T315, Promotes CBL-dependent Degradation of EGFR via Y1045 Autophosphorylation. *Am J Respir Crit Care Med.* 2016 Apr 1;193:753-66.
3. Tseng SJ, Huang KY, Kempson IM, Kao SH, Liu MC, Yang SC, Liao ZX, Yang PC: Remote Control of Light-Triggered Virotherapy. *ACS Nano.* 2016 Nov 22;10(11):10339-10346.
4. Tseng SJ, Kempson IM, Huang KY, Li HJ, Fa YC, Ho YC, Liao ZX, Yang PC: Targeting Tumor Microenvironment by Bioreduction-Activated Nanoparticles for Light-Triggered Virotherapy. *ACS Nano.* 2018 Oct 23;12(10):9894-9902. doi: 10.1021
5. Yang CY, Yang JCH, Yang PC: Precision Management of Advanced NSCLC. *Annu. Rev. Med.* 2020. <https://doi.org/10.1146/annurev-med-051718-013524>

Session I

Biobank and Big Data

Moderator1: (JP) Atsushi Ohtsu, National Cancer Center Hospital East
(TW) Yi-Hsin Connie Yang, National Health Research Institutes

Moderator2: (JP) Kengo Kinoshita, Tohoku University
(TW) Yi-Hsin Connie Yang, National Health Research Institutes

Session I: Biobank and Big Data



Kengo Kinoshita, PhD

Deputy executive director, professor

Tohoku Medical Megabank Organization, Tohoku Univ

Email: kengo@ecei.tohoku.ac.jp

【Profile】

Education and Professional Positions

-Kyoto University, Ph.D, 1999.

-Yokohama City University, Assistant Professor, 2001

-University of Tokyo, Associate Professor, 2004

-Tohoku University, Professor, 2009-

-Tohoku University Tohoku Medical Megabank Organization, Professor, 2012-

-Tohoku University Tohoku Medical Megabank Organization, Deputy Executive Director, 2016-

-The Advanced Research Center for Innovations in Next-Generation Medicine, Deputy Center Director, 2018-

【Professional interests and specialties】

1. Bioinformatics/Computational biology
2. Genome/Omics

【Selected Publications】

1. S. Tadaka, F. Katsuoka, M. Ueki, K. Kojima, S. Makino, S. Saito, A. Otsuki, C. Gocho, M. Sakurai-Yageta, I. Danjoh, IN. Motoike, Y. Yamaguchi-Kabata, M. Shirota, S. Koshihara, M. Nagasaki, N. Minegishi, A. Hozawa, S. Kuriyama, A. Shimizu, J. Yasuda, N. Fuse, the Tohoku Medical Megabank Project Study Group, G. Tamiya, M. Yamamoto, K. Kinoshita, "3.5KJPNv2: an allele frequency panel of 3552 Japanese individuals including the X chromosome". *Hum Genome* 6 (28), 2019.

2. Y. Yamaguchi-Kabata, J. Yasuda, A. Uruno, K. Shimokawa, S. Koshihara, Y. Suzuki, N. Fuse, H. Kawame, S. Tadaka, M. Nagasaki, K. Kojima, F. Katsuoka, K. Kumada, O. Tanabe, G. Tamiya, N. Yaegashi, K. Kinoshita, M. Yamamoto, S. Kure; Tohoku Medical Megabank Project Study Group. "Estimating carrier frequencies of newborn screening disorders using a whole-genome reference panel of 3552 Japanese individuals." *Hum Genet* 138 (4) : 389-409, 2019

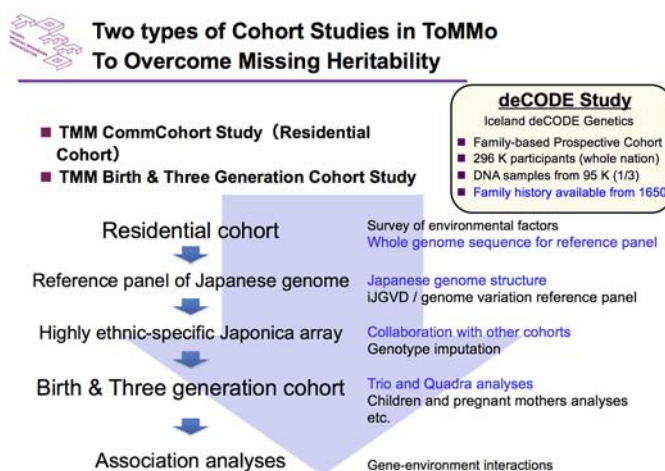
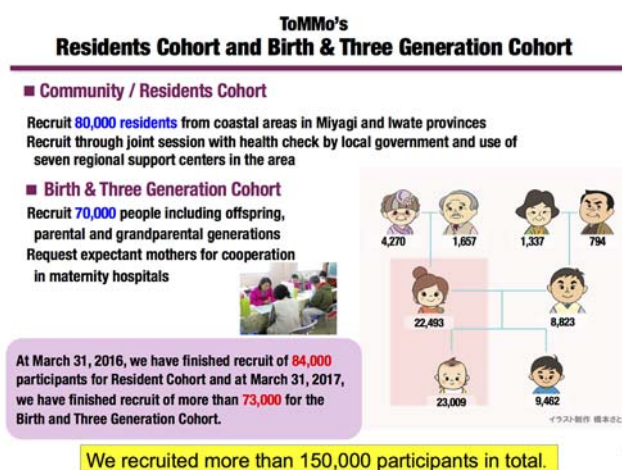
【Abstract】

The Tohoku Medical Megabank (TMM) Project has been collecting specimens and their health-related data from nearly 150,000 individuals in Miyagi and Iwate prefectures; those areas were

heavily damaged by the great eastern Japan Earthquakes and Tsunami on Mar 11, 2011. As a part of this large project, we are performing systematic genome and omics analyses to construct the basis of personalized healthcare for the next generations in this area to realize constructive regeneration from the disaster.

For the purpose, missing heritability is one of the most important issues to be solved. To overcome this problem, we first designed two types of genome cohort studies; the TMM Community-Based Cohort Study with 80k individuals and the TMM Birth and Three-Generation Cohort Study with 70k individuals. The former cohort will be strong to design case control studies and suitable for genome environment interaction analyses, while the latter will be useful for the improvement of genotype imputations by family-based precise phasing.

In this presentation, we will introduce our strategy of genome-omics analyses in TMM, the current status of our progress, and discuss the future perspectives.





Ueng-Cheng Yang (楊永正), Ph.D.

Director

Center for Systems and Synthetic Biology,

National Yang-Ming University

Email: yang@ym.edu.tw

Profile

Dr. Ueng-Cheng Yang was graduated from Dept. of Agricultural Chemistry at National Taiwan University. After he got his Ph.D. degree from Dept. of Molecular Biology at Princeton University, he completed his postdoctoral training in Dept. of Chemistry at Yale University. He then moved back to the National Yang-Ming University in Taiwan, where he established the Bioinformatics Program in year 2002 and the Institute of Biomedical Informatics in year 2007. Both programs are the first such programs in Taiwan. He has been the vice-president of the Asian-Pacific Bioinformatics Network and the officer of the Bioinformatics Society of Taiwan. He is now the Director of the Center for Systems and Synthetic Biology at National Yang-Ming University.

Professional interests and specialties

1. Bioinformatics of biological pathways and regulation
2. Medical informatics on the integration of clinical trial and real world data
3. Biomedical informatics of neurological and psychological disorders and cancers, and microorganisms.

Selected Publications

1. Yang UC, Hsiao TH, Lin CH, Lee WJ, Lee YS, Fann YC (2019) Integrative LHS for precision medicine research: A shared NIH and Taiwan CIMS experience. *Learn Health Sys.* 3, e10071.
2. Lin CH, Chou HI, Yang UC (2018) A Standard-driven Approach for Electronic Submission to Pharmaceutical Regulatory Authorities. *J Biomed Inform.* 79:60-70.
3. Liou JM, Chen CC, Chen MJ, Chen CC, Chang CY, Fang YJ, Lee JY, Hsu SJ, Luo JC, Chang WH, Hsu YC, Tseng CH, Tseng PH, Wang HP, Yang UC, Shun CT, Lin JT, Lee YC, Wu MS; for the Taiwan Helicobacter Consortium. (2013). Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. *The Lancet*, 381(9862):205-213.
4. Wang YT, Huang YH, Chen YC, Hsu CL, Yang UC (2010) PINT: Pathways INtegration Tool. *Nucleic Acids Res.* 38 (Web Server issue):W124-31. (Featured article)

Digital Medicine and Precision Health Management

Lin T-Y.¹, Fang W-N.¹, Li, M-J.¹, Yang, U-C.^{1,2}

¹Center for Systems and Synthetic Biology, ²Institute of Biomedical Informatics,
National Yang-Ming University

Taiwan became an aged society in year 2018. More than 40 % of the population will be 65 or older around the year 2065. Therefore, burden of the health system will become higher and higher. To make a super-aged society sustainable, healthy aging should be encouraged. In fact, the highest realm of traditional Chinese medicine is prevention. This preventive medicine concept is a reachable goal in modern medicine. Because of the development in big data and artificial intelligence (AI), digital medicine and precision health management are feasible.

A digital medicine alliance (DMA) was formed to network people and to facilitate data management and AI research in Taiwan. To solve unmet needs, DMA needs integrated and high quality data. Although it is legal to integrate the biobank data with the health insurance data, it is expensive and inconvenient to do it in a clean room setting. An alternative is to use “my health bank” data. This service was provided by the Ministry of Health and Welfare (MOHW) in Taiwan to the insured. This data source contains not only the insurance claim data from all hospitals, but also has laboratory and image data. This data can integrate with other types of data, such as those from wearable devices or the genomic data, by using the global unique identifier (GUID) under de-identified state. This tool was developed at NIH in USA and was enhanced in Taiwan. Although GUID may not be safer than other methods, this method was used by hospitals, disease registries, biobanks, and government agency. Moreover, this method has been validated by a consortium-based woman cancer biobank. There are over 5-million GUIDs in the server, which account for more than 1/5 of the population in Taiwan. This approach is more suitable for artificial intelligence studies than a clean room approach.

MOHW also provided a software development kit to vendors, so a third party may develop software to collect my health bank data after a proper informed consent process. An insured may authorize the data download from his account to a data repository. To promote the data donation, DMA developed a stroke APP. This program may help users, especially the transient ischemic attack patients, to be aware of a stroke event. On the other hand, DMA added a simple eConsent function to this stroke APP to facilitate the data donation. Taken together, DMA encourages the donation of my health bank data by providing a stroke APP to potential patients. The collected data can be integrated with other data by using GUID under a de-identified state. These data can be used for AI studies and forms the basis of a learning health system.

Session I: Biobank and Big Data



Atsushi Ohtsu, MD, PhD

Director, National Cancer Center Hospital East

Email: aohtsu@east.ncc.go.jp

Dr Atsushi Ohtsu received his MD in 1983 and PhD in 1992 from Tohoku University in Sendai, Japan. From 1992, he has been working at Gastrointestinal Oncology department in National Cancer Center Hospital East excluding the period of his visit to MD Anderson Cancer Center, USA in 1997. In 2012, he has become the Director of Exploratory Oncology Research & Clinical Trial Center (NCC-EPOC), which involves preclinical, TR, and early/exploratory clinical research in NCC. During the period between 2015 and 2016, he had acted as a scientific board member of Japan Agency for Medical Research and Development (AMED). In 2016, he became the Director of National Cancer Center Hospital East. He has published more than 350 articles that have appeared in peer-reviewed journals such as *NEJM*, the *Lancet*, *Journal of Clinical Oncology*, *Lancet Oncology*, and the *Journal of the National Cancer Institute*. Dr. Ohtsu is also acting as a Director of the Japanese Society of Medical Oncology (serving as the chair of international affair committee) and Japanese Cancer Association. He is also serving as a member or advisory expert of various committees in PMDA, MHLW, and MEXT.

Professional interests and specialties

1. Medical Oncology
2. Developmental Therapeutics

Selected Publications

- 1) Shitara K, Özgüroğlu M, Ohtsu A et al; KEYNOTE-061 investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018 Jul 14;392(10142):123-133.

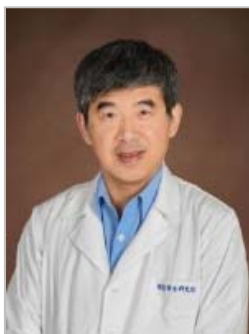
- 2) Kuboki Y, Nishina T, Ohtsu A, et al: TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol* 18(9):1172-1181, 2017
- 3) Yoh K, Seto T, Ohtsu A, et al: Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med*, 5(1):42-50, 2017
- 4) Mayer RJ, Van Cutsem E, Ohtsu A, et al; Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.*; 372(20): 1909-19, 2015
- 5) Ohtsu A, Ajani JA, Bai YX, et al: Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study. *J Clin Oncol.* 31(31):3935-43, 2013
- 6) Yoshino T, Mizunuma N, Ohtsu A, et al: TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol.* 13(10):993-1001, 2012
- 7) Ohtsu A, Shah M, Van Cutsem E, et al: Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. *J Clin Oncol*, 29(30):3968-3976, 2011
- 8) Bang YJ, Van Cutsem E, Ohtsu A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 376: 687-697, 2010
- 9) Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of 5-fluorouracil alone versus 5-fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin C in patients with unresectable advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol*, 21: 54-59, 2003
- 10) Ohtsu A, Boku N, Muro K, et al: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol*, 17:2915-2921, 1999

The nation-wide genome screening platform for new agent developments (SCRUM-Japan): new international project including Asian countries

SCRUM-Japan was launched in 2015 in purpose of facilitating IND registration studies for orphan-fractionated lung/GI cancers with driver/actionable genes as academia-industry collaborations. As of March 2019, more than 10,000 patients (pts) have already been enrolled into the study and their tumor

tissues were analyzed with cutting-edge multi-gene panels followed by referring to 48 molecularly matched umbrella/basket type IND registration studies including 18 investigator-initiated studies. To date, 16 of the 48 registration studies have already been published, which resulted in 5 new agents (6 indications) approval. Genome profiling and clinical outcome data of more than 10,000 pts are being shared on time with 16 pharmaceutical companies and 66 participating institutions, which yielded another new agent/target discovery. New projects using cutting-edge liquid biopsy screening with 73 gene panel was also started in December 2017 and more than 2,000 pts have already been enrolled. With these outcome data and international data integrations, various new evidences/discoveries have been obtained partly from international academia collaborations between Japan and Western countries. Another challenge for making historical control data used in the evaluation of new agent regulatory approval has also started as a quality-controlled prospective registry study. This regulatory-grade registry study is targeted to the subjects with driver genes in which clinical data are converted to CDISC standards. Several registration studies with parallel regulatory-grade control data collection are now underway in collaboration with PMDA.

We launched SCRUM-Asia in 2018 for expanding the genome screening platform to Asian countries. From March 2019, screening from Taiwanese pts was started in Chang-Gung university hospital, which will soon be expanded to 7 hospitals in Taiwan and new participants from China and Singapore. This Asian platform and genomic/clinical data with large sample size will facilitate new agent development/discovery, which may construct actual precision medicine in Asian countries.



Shih-Feng Tsai (蔡世峰), Ph.D.

Director

Department of Research Planning and Development

National Health Research Institutes

Email: petsai@nhri.org.tw

Education

- Ph.D. Division of Human Genetics, Mt. Sinai School of Medicine, City University of New York, USA (1987)
- M.D. Taipei Medical College, Taiwan (1981)

Professional Experiences

- 2017- present Director, Department of Research Planning and Development, National Health Research Institutes, Taiwan
- 2017-2020 Principle Investigator, Flagship Program of Precision Medicine for AsiaPacific Biomedical Silicon Valley
- 2010- present Distinguished Investigator, Institute of Molecular and Genomic Medicine (Formerly Institute of f Molecular and Genomic Medicine), National Health Research Institutes, Taiwan
- 2000-2010 Investigator, Division of Molecular and Genomic Medicine, National Health Research Institutes, Taiwan
- 2000-2007 Director, Division of Molecular and Genomic Medicine, National Health Research Institutes, Taiwan
- 1997- present Professor, Department of Life Sciences and Institute of Genomic Sciences (Formerly Institute of Genetics), National Yang-Ming University, Taiwan
- 1991-1997 Associate Professor, Institute of Genetics, National Yang-Ming University, Taiwan
- 1988-1990 Fellow, Department of Pediatrics, Harvard Medical School, U.S.A
- 1988-1990 Fellow, Division of Hematology/Oncology, Children's Hospital, U.S.A.
- 1987-1988 Fellow, Division of Medical Genetics, Mt. Sinai Medical Center, U.S.A.

Publications

1. Huang TW, Lam I, Chang HY, Tsai SF, Palsson BO, Charusanti P. Capsule deletion via a λ -Red knockout system perturbs biofilm formation and fimbriae expression in *Klebsiella pneumoniae* MGH 78578. (2014) *BMC Res Notes*. 7:13. doi: 10.1186/1756-0500-7-13.
2. Sun WS, Syu WJ, Ho WL, Lin CN, Tsai SF, Wang SH. SitA contributes to the virulence of *Klebsiella pneumoniae* in a mouse infection model. (2014) *Microbes Infect*. 16(2):161-70. doi: 10.1016/j.micinf.2013.10.019.
3. Lee SH, Li CF, Lin HY, Lin CH, Liu HC, Tsai SF, Niu DM. High-throughput detection of common

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4. Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, Chen MJ, Lin JY, Hui RC, Ho JC, Wu WM, Chen TJ, Wu T, Wu YR, Hsieh MS, Tu PH, Chang CN, Hsu CN, Wu TL, Choon SE, Hsu CK, Chen DY, Liu CS, Lin CY, Kaniwa N, Saito Y, Takahashi Y, Nakamura R, Azukizawa H, Shi Y, Wang TH, Chuang SS, Tsai SF, Chang CJ, Chang YS, Hung SI; Taiwan Severe Cutaneous Adverse Reaction Consortium; Japan Pharmacogenomics Data Science Consortium. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. (2014) *JAMA.* 6;312(5):525-34. doi: 10.1001/jama.2014.7859.
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 7. Huang TW, Lauderdale TL, Liao TL, Hsu MC, Chang FY, Chang SC, Khong WX, Ng OT, Chen YT, Kuo SC, Chen TL, Mu JJ, Tsai SF. Effective transfer of a 47 kb NDM-1-positive plasmid among *Acinetobacter* species. (2015) *J Antimicrob Chemother.* 70(10):2734-8.
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 9. Liu YC, Wang SC, Yu YJ, Fung KM, Yang MT, Tseng YH, Tsai SF, Sun HS, Lyu PC, Chou SH. Complete Genome Sequence of *Xanthomonas campestris* pv. *campestris* Strain 17 from Taiwan. (2015) *Genome Announc.* 17;3(6). pii: e01466-15.
 10. Lai JH, Yang JT, Chern J, Chen TL, Wu WL, Liao JH, Tsai SF, Liang SY, Chou CC, Wu SH. Comparative Phosphoproteomics Reveals the Role of AmpC β -lactamase Phosphorylation in the Clinical Imipenem-resistant Strain *Acinetobacter baumannii* SK17. (2016) *Mol Cell Proteomics.* 15(1):12-25.
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 16. Ho CH, Tsai SF. Functional and biochemical characterization of a T cell-associated anti-apoptotic protein, GIMAP6. (2017) *J Biol Chem.* 292(22):9305-9319.
 17. Fang CT, Yi WC, Shun CT, Tsai SF. DNA adenine methylation modulates pathogenicity of *Klebsiella*

- pneumoniae genotype K1. (2017) *J Microbiol Immunol Infect.* 50(4):471-477.
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 19. Lin RK, Hung WY, Huang YF, Chang YJ, Lin CH, Chen WY, Chiu SF, Chang SC, Tsai SF. Hypermethylation of *BEND5* contributes to cell proliferation and is a prognostic marker of colorectal cancer. (2017) *Oncotarget.* 8(69):113431-113443.
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 21. Huang CH, Chang YH, Lin CY, Wang WH, Kuan HC, Hsieh YJ, Wang YW, Yang CH, Chiu JY, Tsai SF, Chen YH, Liu HH. Shared IgG Infection Signatures vs. Hemorrhage-Restricted IgA Clusters in Human Dengue: A Phenotype of Differential Class-Switch via *TGFβ1*. (2017) *Front Immunol.* 8:1726.
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 23. Liu JY, Liao TL, Huang WC, Liu YM, Wu KM, Lauderdale TL, Tsai SF, Kuo SC, Kuo HC. Increased *mcr-1* in pathogenic *Escherichia coli* from diseased swine, Taiwan. (2018) *J Microbiol Immunol Infect.* pii: S1684-1182(18)30193-2.

Big Data Analysis for Cancer and Rare Disease

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Institute of Molecular and Genomic Medicine
National Health Research Institutes
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To implement precision medicine in Taiwan, we have designed a four-year development scheme to promote industrial development that can offer new products and services to benefit the patients. A research network, which includes four medical centers in northern, central, southern, and eastern Taiwan, has been established to identify significant issues to be tackled on by genomic technology. In the first two years we have focused on establishing a high-throughput DNA sequencing capacity with four units of NovaSeq 6000 sequencers to provide whole-genome and whole-exome sequencing and RNA sequencing services to the researchers. Initially we focused on the study of rare disease and cancer, and we have so far sequenced over two thousands genomes for the Taiwanese patients. These cover rare disease patients and their family members, and cancer patients with paired samples (tumor and control). For rare diseases, we selected cases that have previously exhausted all the molecular diagnostics methods without a genetic diagnosis, including those of immunodeficiency, epilepsy, spinocerebellar ataxia, hearing impairment, Rett syndrome, familial cancer, and general undiagnosed disease. For cancer, we supported the investigation on liver cancer (hepatocellular carcinoma), lung cancer (adenocarcinoma), upper tract urothelial carcinoma (UTUC), breast cancer, leukemia, and other types of cancer. In this presentation, I will showcase the results of two pedigrees with familial cancer (endometrial carcinoma and gastric cancer) and the results of a comparative analysis between UTUC patients of Taiwan and Japan.

Session I: Biobank and Big Data

Yoji Nagai, MD, PhD

Professor and Director
Clinical & Translational Research Center
Kobe University Hospital

Profile

Nagai studied pharmaceutical sciences at The University of Tokyo (1982 -1987) and medicine at Osaka University Medical School (1987–1991). After completing his residency, he worked as a stroke neurologist at Hoshigaoka Medical Center (1992-1996) and later at Osaka University Hospital (1998-2003). As a Visiting Fellow at the National Institutes of Health in the US (1996-1998), he engaged in a large clinical study and received relevant training. Subsequently, he worked at the Translational Research Informatics Center of the Foundation for Biomedical Research & Innovation, primarily committed to the management of clinical studies and governmental translational research center programs (2003-2015). Since 2015, he has been at Kobe University Hospital, working to strengthen the organization system for promoting clinical and translational research, and to facilitate individual research projects.

Professional interests and specialties

1. Clinical studies
2. Translational researches

Selected Publications

1. Kojima S, Murotani K, Zhou B, Kothari KU, Fukushima M, Nagai Y. Assessing long term care risk in elderly individuals with possible cognitive Decline: A large population-based study using the "Kihon Checklist. *Geriatr Gerontol Int*. 2019;19:598-603
2. Zhou B, Zhao Q, Kojima S, Ding D, Higashide S, Nagai Y, Guo Q, Kagimura T, Fukushima M, Hong Z. One-year outcome of Shanghai mild cognitive impairment cohort study. *Current Alzheimer Research* 2019;16:156-165.

Abstract

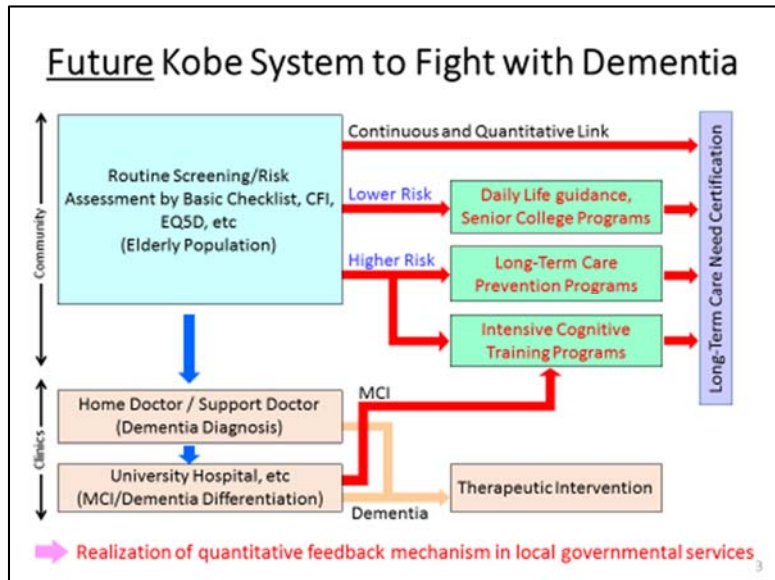
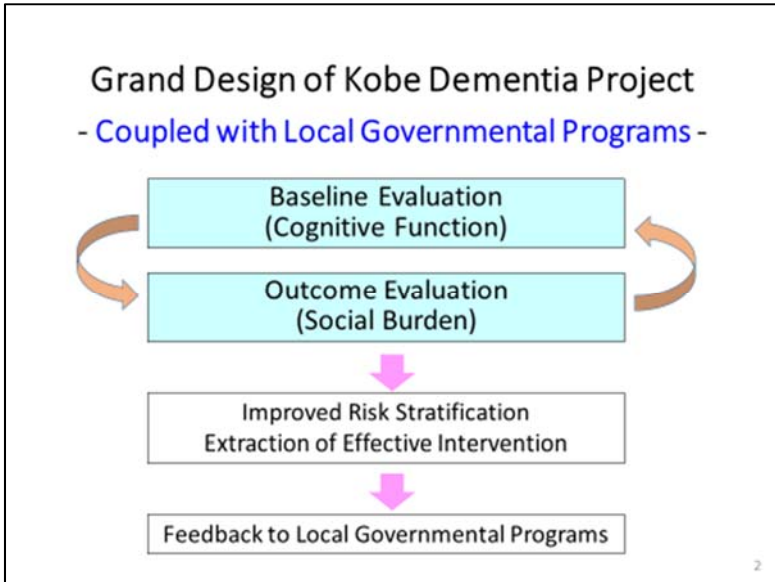
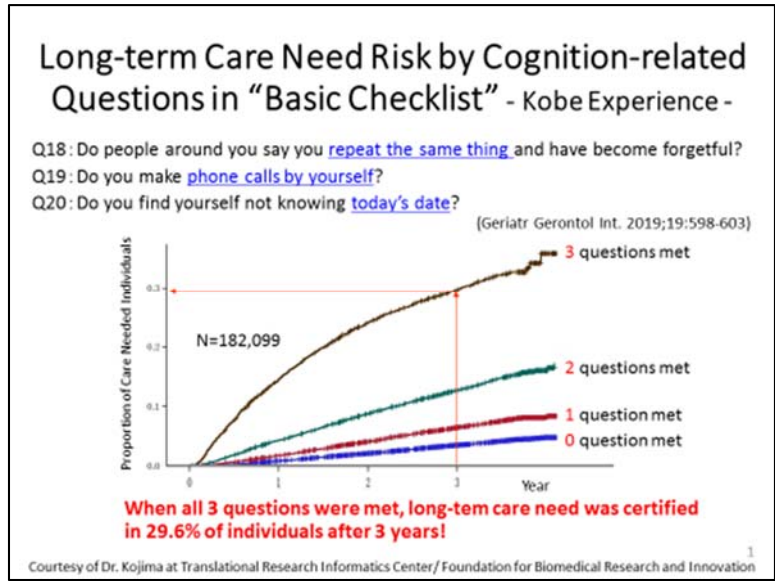
Kobe Project for the Exploitation of Newer Strategies to Reduce Social Burden of Dementia

Plunging into the unprecedented super-aged society, reduction of the social burden for Long-Term Care (LTC) is a pressed challenge of the nation. Particularly, dementia is one of the leading causes for care-requiring status, accounting for 20% of individuals in LTC. Given the absence of effective treatments for dementia, earlier identification of individuals at risk and earlier interventions thereby could potentially slow the process of cognitive decline, preventing the transition to dementia. However, such approaches have achieved only a limited success, in part due to the lack of efficient social mechanism to identify individuals at risk.

Under such conditions, we have examined predictive value of “Kihon Checklist” (KCL) and the 3 cognitive domain therein for incident LTC need certification, on 182,099 citizens in Kobe. KCL is a self-reported frailty questionnaire, which had been widely delivered to citizens from the local governments across the nation. We have found that each unfavorable answer on the 3 cognitive domain was associated with the risk for LTC need, independent of age, sex and other items on KCL. Of note, as the number of unfavorable answers to the cognitive domain increased from 0 to 1, 2 and 3 at baseline, the incidence of LTC need progressively increased from 3.5% to 6.4%, 12.6%, and 29.6% after 3 years, suggesting the potential utility of a simple questionnaire for earlier detection of individuals at risk.

Spurred by the findings, we have started the current project, under the collaboration of Kobe University, WHO Kobe Center and Foundation for Biomedical Research and Innovation, given robust supports from the Kobe city. The project includes 3 population based studies, in which baseline data collection was completed, waiting for the connection with LTC need certification data in the next year. Through this project, we are expecting a condition, in which screening and risk assessment for dementia is regularly done with the use of simple questionnaire, as part of the local governmental system, and the risk is continuously monitored in relation to LTC need. Thus, the final goal of this project is to lay foundation for constructing such a feedback mechanism in the local governmental services, for the reduction of social burden of dementia.

Presentation Slides



Session I: Biobank and Big Data



Jack Yu-Chuan Li (李友專), MD, PhD

Distinguished Professor, Graduate Institute of Biomedical Informatics, CoMST, TMU
Dean, College of Medical Science and Technology, Taipei Medical University
Chair, Dept. of Dermatology, Taipei Medical University. Wan Fang Hospital
Email: jack@tmu.edu.tw

EDUCATION / TRAINING

(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
School of Medicine, University of Utah	Ph.D.	1994	Medical Informatics
Taipei Medical University, Taipei, Taiwan	M.D.	1991	Medicine

Personal Website : jackli.cc

A. Personal Statement

Prof Dr. Yu-Chuan (Jack) Li has been a pioneer of Medical Informatics research in Asia. He served as a Vice President of Taipei Medical University (TMU) (2009-2011) and currently, he has been the Dean of College of Medical science and Technology since 2011 and Distinguished Professor of the Graduate Institute of Biomedical Informatics since 1998. He obtains his M.D. from TMU in 1991 and his PhD in Medical Informatics from University of Utah in 1994. Due to his achievement in establishing EHR exchange models among hospitals and his dedication to IT applications in patient safety and care, he was awarded as one of the Ten Outstanding Young Persons of the Year in 2001. He has been Principal Investigator of many national and international projects in the domain of Electronic Health Record, Patient Safety Informatics and Medical Big Data. He is author of 130 scientific papers and 3 college-level textbooks. He became an elective fellow of American College of Medical Informatics (FACMI), (2010), Australian College of Health Informatics (FACHI), (2010), founding members of International Academy of Health Sciences Informatics (IAHSI), (2017) and also the President of Asia Pacific Association for Medical Informatics (APAMI) from 2006 to 2009. Currently, he is the Editor-in-Chief of two internationally renowned journals - Computer Methods and Programs in Biomedicine and International Journal for Quality in Health Care. His main areas of expertise are: AI in Medicine, Patient Safety Informatics, and Medical Big Data Analytics.

B. Positions and Honors

1. Positions and Employment

- 2017— Associate Editor, JCO Clinical Cancer Informatics (JCOCCI)
- 2016— Distinguished Professor, Graduate Institute of Biomedical Informatics, CoMST, TMU
- 2014— Editor-in-Chief, International Journal for Quality in Health Care (IJQHC)
- 2013— Editor-in-Chief, Journal of Computer Methods and Programs in Biomedicine (CMPB)
- 2011— Dean, College of Medical Science and Technology, Taipei Medical University, Taiwan
- 2009— Chair Dermatologist, Dept. of Dermatology, Taipei Medical University. Wan Fang Hospital, Taiwan
- 2009— Professor, Graduate Institute of Biomedical Informatics, Taipei Medical University, Taiwan

2009— Adjunct Professor, Dept. of Biomedical Informatics, National Yang-Ming University, Taiwan

2. Academic Honors

2017 International Academy of Health Sciences Informatics (IAHSI)

2010 American College of Medical Informatics (FACMI), US

2010 Australian College of Health Informatics (FACHI), Australia

2001 The 39th Ten Outstanding Young Persons, Taiwan

C. Selected Publications

1. Chieh-Chen Wu, Wen-Ding Hsu, Md. Mohaimenul Islam, Tahmina Nasrin Poly, Hsuan-Chia Yang, Phung-Anh (Alex) Nguyen, Yao-Chin Wang, **Yu-Chuan(Jack) Li***(2019, Jan). An artificial intelligence approach to early predict non-ST-elevation myocardial infarction Patients with Chest Pain. *Computer Methods and Programs in Biomedicine*, (Accepted)
2. Chieh-Chen Wu, Wen-Chun Yen, Wen-Ding Hsu, Md. Mohaimenul Islam, Phung Anh (Alex) Nguyen, Tahmina Nasrin Poly, Yao-Chin Wang, Hsuan-Chia Yang, **Yu-Chuan(Jack) Li***(2019, Mar). Prediction of Fatty Liver Disease using Machine Learning Algorithms. *Computer Methods and Programs in Biomedicine*, 170:23-29
3. Md. Mohaimenul Islam, Tahmina Nasrin Poly, Bruno Andreas Walther, Chieh-Chen Wu, Hsuan-Chia Yang, **Yu-Chuan(Jack) Li***(2019, Mar). Prediction of Sepsis Patients Using Machine Learning Approach: A Meta-Analysis. *Computer Methods and Programs in Biomedicine*, 170:1-9
4. Chu-Ya Huang, Phung-Anh Nguyen, Hsuan-Chia Yang, Md Mohaimenul Islam, Chia-Wei Liang, Fei-Peng Lee, **Yu-Chuan (Jack)Li***(2019, Mar). A Probabilistic Model for Reducing Medication Errors: A Sensitivity Analysis using data in Electronic Health Records *Computer Methods and Programs in Biomedicine*, 170:31-38
5. Usman Iqbal, Ayesha Humayun, **Yu-Chuan (Jack) Li***(2019, Feb). Healthcare quality-improvement and measurement strategies and its challenges ahead. *International Journal for Quality in Health Care*, 31(1):1
6. Md.Mohaimenul Islam, Tahmina Nasrin Poly, Bruno Andreas Walther, Navneet Kumar Dubey, Dina Ningrum, Shabbir Syed Abdul, **Yu-Chuan (Jack) Li***(2019, Feb). "Response to letter: 'Proton pump inhibitors therapy and the risk of major osteoporotic nonhip fractures in older adults in Taiwan" *European Journal of Gastroenterology & Hepatology*, 31(2):276
7. Rayleigh Ping-Ying Chiang*, Chien-Fu Lin, Yu-Chuan (Jack) Li, Min-Huei Hsu (2019, Feb). The Importance of Sleep for Governmental Sectors, General Population and Industry – Asia-Pacific Economic Cooperation (APEC) Sleep Technology Agenda. *Sleep Medicine Reviews*, 43:135-136
8. Chih Yuan Wu, Chih-Wei Huang, Hsuan-Chia Yang, **Yu-Chuan (Jack) Li***(2019, Jan). Opportunities and challenges in Taiwan for implementing the learning health system. *International Journal for Quality in Health Care*,
9. Hsuan-Chia Yang, Tahmina Nasrin Poly, **Yu-Chuan (Jack) Li***(2019, Jan). Deep into Patient care: An automated deep learning approach for reshaping patient care in clinical setting. *Computer Methods and Programs in Biomedicine*, 168: A1-A2
10. Tahmina Nasrin Poly, Md.Mohaimenul Islam, Hsuan-Chia Yang, Chieh-Chen Wu, **Yu-Chuan (Jack) Li***(2019, Jan). Proton Pump Inhibitors and risk of Hip fracture: A Meta-analysis of Observational Studies. *Osteoporosis International*, 30(1):103-114
11. Tahmina Nasrin Poly, Md. Mohaimenul (Rubel) Islam, Hsuan-Chia Yang, **Yu-Chuan Jack Li***(2019, Jan). Non-steroidal anti-inflammatory drugs and risk of Parkinson's disease in the elderly population: a meta-analysis. *European Journal of Clinical Pharmacology*, 75(1): 99-108
12. Md.Mohaimenul Islam, Tahmina Nasrin Poly, Hsuan-Chia Yang, Chieh-Chen Wu, **Yu-Chuan (Jack) Li** (2019). Increase Risk of Multiple Sclerosis in Patients with Psoriasis Disease: An Evidence of Observational Studies. *Neuroepidemiology*, 52:152–160

13. Phung Anh Nguyen, Hsuan-Chia Yang, Rong Xu, **Yu-Chuan (Jack) Li** (2018). An Automated Technique to Construct a Knowledge Base of Traditional Chinese Herbal Medicine for Cancers: An Exploratory Study for Breast Cancer. *Studies in health technology and informatics* 247: 661-665
14. Hsuan-Chia Yang, Md. Mohaimenul Islam, **Yu-Chuan (Jack) Li*** (2018, Dec). Development of user-friendly tools for biomedical research and healthcare. *Computer Methods and Programs in Biomedicine*, 167: A1
15. Hsuan-Chia Yang, Phung Anh (Alex) Nguyen, Md. Mohaimenul Islam, Chih-Wei Huang, Tahmina Nasrin Poly, Usman Iqbal, **Yu-Chuan (Jack) Li*** (2018, Dec). Gout drugs use and risk of cancer: A case-control study. *Joint Bone Spine*, 85(6): 747-753
16. Yao-Chin Wang, Bilegjin Ganzorig, Chieh-Chen Wu, Usman Iqbal, Hafash-Arshed-Ali Khan, Wan-Shan Hsieh, Wen-Shan Jian, **Yu-Chuan (Jack) Li*** (2018, Dec). Patient satisfaction with dermatology teleconsultation by using MedX. *Computer Methods and Programs in Biomedicine*, 167:37-42
17. Santiago Hors-Fraile, Shwetambara Malwade, Dimitris Spachos, Luis Fernandez Luque, Chien-Tien Su, Wei-Li Jeng, Shabbir Syed-Abdul*, Panagiotis Bamidis, Yu-Chuan (Jack) Li (2018, Nov). A recommender system to quit smoking with mobile motivational messages: study protocol for a randomized controlled trial. *Trials*, 19(1): 618
18. Phung-Anh Nguyen, Yu-Chuan (Jack) Li* (2018, Nov). Artificial Intelligence in Clinical Implications. *Computer Methods and Programs in Biomedicine*, 166: A1
19. Chung-Ming Lo, Yu-Chuan (Jack) Li* (2018, Oct). The use of multimedia medical data and machine learning for various diagnoses. *Computer Methods and Programs in Biomedicine*, 165: A1
20. Navneet Kumar Dubey*, Dina Nur Anggraini Ningrum*, Rajni Dubey*, Yue-Hua Deng*, **Yu-Chuan Li***, Peter D. Wang*, Joseph R. Wang*, Shabbir Syed-Abdul*, Win-Ping Deng* (2018, Oct). Correlation between Diabetes Mellitus and Knee Osteoarthritis: A Dry-To-Wet Lab Approach. *International Journal of Molecular Sciences*, 19(10), 3021
21. Ming-Chin Lin, Usman Iqbal, **Yu-Chuan Jack Li*** (2018, Oct). AI in Medicine: Big Data Remains a Challenge. *Computer Methods and Programs in Biomedicine*, 164: A1
22. Phung-Anh (Alex) Nguyen, Yao-Chin Wang, **Yu-Chuan (Jack) Li*** (2018, Sep). The role of informatics in improving patient care. *Computer Methods and Programs in Biomedicine*, 163: A1
23. Saurabh Singh Thakur*, Shabbir Syed Abdul*, Hsiao-Yean (Shannon) Chiu*, Ram Babu Roy*, Po-Yu Huang*, Shwetambara Malwade*, Aldilas Achmad Nursetyo*, **Yu-Chuan (Jack) Li*** (2018, Aug). Artificial-Intelligence-Based Prediction of Clinical Events among Hemodialysis Patients Using Non-Contact Sensor Data. *Sensors*, 18(9), 2833
24. Md. Mohaimenul Islam, Tahmina Nasrin Poly, **Yu-Chuan (Jack) Li*** (2018). Recent Advancement of Clinical Information Systems: Opportunities and Challenges. *IMIA yearbook*, 27(01): 083-090

An AI Perspective on Individualized Cancer Risk

Yu-Chuan(Jack) Li

Graduate Institute of Biomedical Informatics, College of Medical Science and Technology, Taipei Medical University

Artificial Intelligence (AI) has had a great impact on the healthcare field and will continue to transform health systems radically. In light of the AlphaGo program that wins over two of the best Go chess players in the world, AI is now back to the spotlight again. Given advice and warnings from some of the top minds like Elon Musk and the late Steven Hawking, it seems inevitable that AI is going into a fast-paced development in the next few years and likely to impact every aspect of our lives soon. This talk will describe some of the most important AI applications in healthcare, namely, prediction and early detection of cancers. This can lead to the future of individualized prevention for cancers and major illness like stroke, dementia...etc. We will also discuss why Big Data AI will go hand-in-hand into the future of health care for all the stakeholders, in terms of high-performance healthcare and precision medicine.

Session II

Big Data

Moderator: (JP) Yoji Nagai, Kobe University

(TW) Ueng-Cheng Yang, National Yang-Ming University

Session II: Big Data



Bin Zhou, MD, PhD

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Translational Research Center for
Medical Innovation
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Risk factors of dementia in subjects with cerebral vascular disease based on big data

Bin Zhou research interest is the methodology in clinical and translational research, particularly in neurological diseases. Now she is focusing on the clinical research of Alzheimer's Disease (AD), to identify the risk and protective factors and to establish the clinical trial design methods of prevention and treatment for AD.

The effect of statin on dementia and cognition has been controversial for a long time. Some studies indicated the use of statins may benefit patients with Alzheimer Disease. While some researches think statins don't support a preventive effect of late-life station us eon cognition decline based several RCT and observational studies. FDA warned stain-related reversible cognitive impairment. We use Taiwan health insurance data to explore the relationship of statins and other factors in subjects of cerebral vascular disease without mention cerebral infarction. We found that the total statins showed to decrease the risk of dementia, however no single statin benefited for people at risk. Osteoporosis and depression increased the risk of dementia. The ADNI data indicated Lipitor is associated with higher risk of AD in beta amyloid positive subjects with mild cognitive impairment and normal cognition.

Professional interests and specialties

1. Neurology, Cognition disorder
2. Methodology of Clinical and translational research


Selected Publications

3. Zhou B, Zhao Q, Kojima S, Ding D, Nagai Y, et al. one-year outcomes of Shanghai mild cognitive impairment cohort study. *Current Alzheimer Disease*. 2019, 16(2):156-165.
4. Zhou B, Zhao Q, Kojima S, Ding D, Nagai Y, et al. Shanghai cohort study on mild cognitive impairment---study design and baseline characteristics. *Journal of Alzheimer disease & Parkinsonism*. 2016,6:224.
5. Zhou B. Prevention strategies targeting different preclinical stages of Alzheimer's disease. *Current Alzheimer Disease*. 2015,12(6):504-506.

Presentation Slides

5th Taiwan-Japan ARO workshop, Sendai, Sep.26,2019

Risk factors of dementia in subjects with cerebral vascular disease based on big data



Bin Zhou
Translational Research Center for Medical Innovation (TRI)

5th Taiwan-Japan ARO, Sendai 1

Figure 1 Database and subjects

NHIRD[※], provided by the Bureau of National Health Insurance (BNHI)
 ※ NHI research data

LHID2000[※], 1 million beneficiaries randomly selected from the NHIRD
 ※ Longitudinal Health Insurance Database 2000

4207 cases, year 2000-2013
 (433)occlusion and stenosis of precerebral arteries, (434) cerebral arteries, (435)transient cerebral ischemia (4370)cerebral atherosclerosis Without mention cerebral infarction

Follow-up(2000-2013), average 5.15(SD:3.79) years

5th Taiwan-Japan ARO, Sendai 2

Table 1. Distributions of Demographic and Clinical Comorbid Status in Study Cohorts

Variable Subtype	All N=4207		Conversion to dementia N=392		Non-conversion N=3815		P value*
	N (%)	n (%)	n (%)	n (%)			
Occlusion and stenosis of precerebral arteries (433)	914(21.7)	66 (16.8)	848 (22.2)	0.01			
Occlusion of cerebral arteries (434)	243(5.78)	26 (6.69)	217 (5.69)	0.45			
Transient cerebral ischemia (435)	2645(62.9)	270 (68.9)	2375 (62.3)	0.01			
Cerebral atherosclerosis (4370)	405(9.63)	30 (7.65)	375 (9.83)	0.16			
Sex				0.08			
Female	1861(44.2)	190 (48.5)	1671 (43.8)				
Male	2346(55.8)	202 (51.5)	2144 (56.2)				
Age group (year)				<0.001			
40-64	1623(38.6)	56 (14.3)	1567 (41.1)				
65-74	1199(28.5)	137 (35.0)	1062 (27.8)				
≥ 75	1385(32.9)	199 (50.8)	1186 (31.1)				
Age (year), mean (standard deviation) †	68.1(12.0)	74.4 (8.73)	67.5 (12.2)	<0.001			
Average follow-up years	5.15(3.79)	3.50 (2.80)	5.32 (3.83)	<0.001			

5th Taiwan-Japan ARO, Sendai 3

Table 2. HR of dementia in Association with Sex, Age, Comorbidities, and Medications in Univariable and Multivariable Cox Regression Models

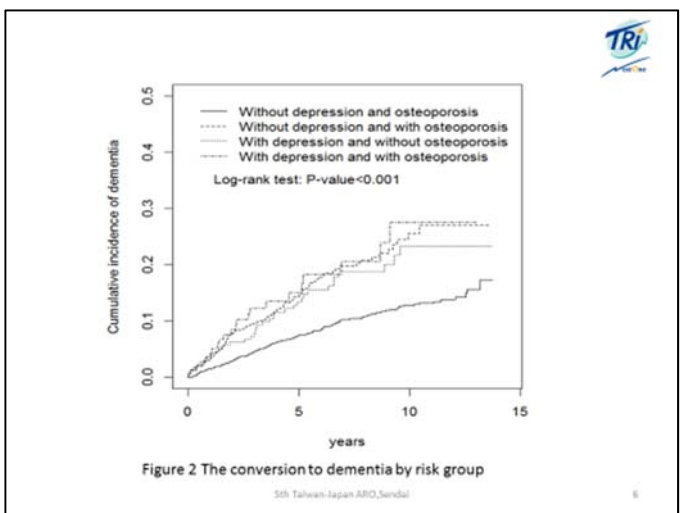
Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Age group (year)				
40-64	1.00	(Reference)	1.00	(Reference)
65-74	3.82	(2.80, 5.21)***	3.57	(2.59, 4.92)***
≥ 75	6.55	(4.86, 8.83)***	5.76	(4.20, 7.91)***
Comorbidities before index date				
Diabetes mellitus (250)	1.12	(0.89, 1.40)		
Hypertension (401-405)	1.60	(1.20, 2.12)**		
Hyperlipidemia (272)	0.92	(0.75, 1.12)		
Coronary heart disease (410-414)	1.33	(1.09, 1.62)**		
Osteoporosis (733)	2.01	(1.62, 2.49)***	1.49	(1.18, 1.88)***
Head injury (310.2, 800, 801, 803, 804, 850-854, and 959.01)	1.21	(0.88, 1.66)		
Depression(296.2, 296.3, 300.4, and 311)	1.70	(1.30, 2.23)***	1.68	(1.26, 2.23)***
Sleep disorder(307.4 and 780.5)	1.30	(1.06, 1.59)*		

5th Taiwan-Japan ARO, Sendai 4

Table 2. HR of dementia in Association with Sex, Age, Comorbidities, and Medications in Univariable and Multivariable Cox Regression Models (Continue)

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Medications				
Probuocol use	1.52	(0.38, 6.08)		
Statin	0.58	(0.48, 0.71)***	0.74	(0.60, 0.92)**
Aspirin	1.07	(0.73, 1.56)		
Clopidogrel	0.86	(0.70, 1.07)		
Hydralazine	1.30	(1.06, 1.59)*	1.14	(0.92, 1.40)
Nitroglycerin	0.82	(0.67, 0.99)*	0.70	(0.56, 0.88)**
Nitroprusside Sodium	1.54	(0.73, 3.25)		
Thrombolysis	0.53	(0.35, 0.81)**	0.68	(0.39, 1.17)
Stent	0.57	(0.36, 0.91)*	0.91	(0.50, 1.63)

5th Taiwan-Japan ARO, Sendai 5





Yang C. Fann (范揚政), Ph.D.

Director

Intramural IT and Bioinformatics Program

National Institute of Neurological Disorders and Stroke (NINDS)

National Institutes of Health (NIH)

Email: fann@mail.nih.gov

EDUCATION / TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Temple University, Philadelphia, PA	Ph.D.	1992	Computational Chemistry
Northwestern University, IL	Postdoc	1994	Structure Biology
Washington Univ. in St. Louis, MO	Research Associate	1996	Computational Biology

A. Positions and Honors

Position and Employment

- 1997-2001 Senior Scientific Task Manager, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC
- 2002- Director, Intramural IT and Bioinformatics Program, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD
- 2009 Principle Investigator, Informatics Core, DoD/NIH Center for Neuroscience and Regenerative Medicine (CNRM) for National TBI Research Program

Other Appointments and Professional Memberships

- 2002-present NCBI/NIH Bioinformatics Core Faculty
- 2003-present Member, NIH IT Management Committee
- 2003-present Member, Health Level Seven (HL7), Regulated Clinical Research Information Management
- 2007-present Co-chair, Translational Research Information System (TRIS) Steering Committee
- 2010-present PI, Informatics Core, Center for Neuroscience and Regenerative Medicine (CNRM), USUHS
- 2010-present Member, NHGRI Microarray Core Steering Committee, NIH, Bethesda, MD
- 2012-present Member, NIH Biomedical Informatics Coordination (BIMC) Working Group
- 2012-present Member, NIH High performance Computing Working Group
- 2012-present Member, Clinical Center IT Advisory Group (ITAG), NIH, Bethesda, MD.
- 2014-present Member, NIH Director's IT Budget Advisory Council
- 2014-present Associate Editor, Computer Methods and Programs in Biomedicine, Elsevier Publisher.

Honors and Awards

1990	Swern Fellowship Award (Temple Univ.)
1991	Guy Allen Outstanding Teaching Award (Temple Univ.)
1992	University Honor of Dissertation Completion Fellowship (Temple Univ.)
1998-2002	Annual Outstanding Management and Performance Award (ITSS/NIEHS)
2005-12	NINDS/NIH Director's Group Merit Awards for various IT and Biomedical Informatics

Projects

2008	Bio-IT World Best Practice Award for Clinical Research
2008/12/13/14	NIH Director's Awards
2010	HHS Secretary's First Innovates Award
2012	NIH Office of Director's Honor Award
2013	NIH Executive Leadership Program
2014	HHS Green Champion Leadership Awards
2015	NIH CIT Director Award on Biomedical Research System Innovations
2017	Bio-IT World Best Practice Award for IBIS (Judge's Choice)

B. Selected Peer-Reviewed Publications

1. Vivek Navale, Michele Ji, Olga Vovk, Leonie Misquitta, Tsega Gebremichael, Alison Garcia, Yang Fann, Matthew McAuliffe; "Development of an informatics system for accelerating biomedical research"; *F1000Research*, 2019, 8:1430 (<https://doi.org/10.12688/f1000research.19161.1>)
2. Kazumasa Unno; Angelos Oikonomopoulos, Yusuke Fujikawa, Yusuke Okuno, Singo Narita, Tomohiro Kato, Ryo Hayashida, Kazuhisa Kondo, Rei Shibata, Toyoaki Murohara, Yanfei Yang, Seema Dangwal, Konstantina-Ioanna Sereti; Qiu Yiling, Kory R Johnson, Alok Kumar Jha, David E Sosnovik, Yang C Fann, Ronglih Liao, "Alteration in ventricular pressure stimulates cardiac repair and remodeling", *J Mol Cell Cardiol.* 2019 Aug;133:174-187. doi: 10.1016/j.yjmcc.2019.06.006. Epub 2019 Jun 17.
3. Ueng-Cheng Yang, Tzu-Hung Hsiao, Ching-Heng Lin, Wei-Ju Lee, Yu-Shan Lee, Yang C. Fann; "Integrative LHS for precision medicine research: A shared NIH and Taiwan CIMS experience", *Learn Health Sys.* 2019;3:e10071. <https://doi.org/10.1002/lrh2.10071>
4. Fann, Y.C. "Enhancing patient care and outcomes through innovative informatics systems and tools", *Comp. Meth. and Prog. in Biomed.* 158, A1 (2018)
5. Jung-Chun Lin; Yuan-Chii Lee; Tse-Hua Tan; Yu-Chih Liang; Huai-Chia Chuang; Yang C. Fann; Kory R. Johnson; Ying-Ju Lin "RBM4-SRSF3-MAP4K4 splicing cascade modulates the metastatic signature of colorectal cancer cell" *BBA - Molecular Cell Research*, v1865, p259-272 (2018)
6. Vivek Navale, Michelle Ji, Evan McCreedy, Tsega Gebremichael, Alison Garcia, Leonie Misquitta, Ching-Heng Lin, Yang C. Fann*, Matthew McAuliffe*, "Standardized Informatics Computing Platform for Advancing Biomedical Discovery Through Data Sharing", *BioRxiv Journal*, 259465, 2018
7. Lin, HC, Yang UC, Fann, YC, "System and method of standard-compliant electronic case report form design and clinical data set generation", *US Patent App.* 15/470,467, 2018

8. Xinjing Wang; Wadiah M Zein ; Leera D'Souza; Chimere Roberson; Keith Wetherby; Hong He; Angela Villarta; Amy Turriff; Kory R Johnson; Yang C Fann, "Applying next generation sequencing with microdroplet PCR to determine the disease-causing mutations in retinal dystrophies" *BMC Ophthalmology*, 17, 157 (2017). PMID: 28838317
9. Jung-Chun Lin, Yuan-Chii Lee, Yu-Chih Liang, Yang Fann, Kory Johnson, and Ying-Ju Lin; "The impact of the RBM4-initiated splicing cascade on modulating the carcinogenic signature of colorectal cancer cells", *Nature Scientific Report*, 7, 44204; doi: 10.1038/srep44204 (2017)
10. Xianlai Chen; Yang C Fann; Matthew McAuliffe; David Vismer; Rong Yang; "Checking Questionable Entry of Personally Identifiable Information Encrypted by One-Way Hash Transformation", *JMIR Medical Informatics*, 5(1), e2, 2017 (PMID 28213343)
11. Lin, C.H., Fann, Y.C. Liou, D.M. "An exploratory study using an openEHR two level modeling approach to represent common data elements", *J. Am. Med. Info. Assoc.* v0. Pp1-12, 2016.
12. Hung, JF, Rau, HH, Hsu, CY, Chen, SC, Tsai, DJ, Fann, YC, Joshua Park, J., Eng, J. "Implementing Globally Unique Identifier Architecture in Date Collection for a Health Management Study in Taiwan Aboriginal Tribe", *Book Chapter of Future Information Technology – II*, p.121-130 2015
13. Yang, Cheng-I, Fann, Yang, Liu, Chien-Tsai, "A MVC Based User Interface Design For Clinical Research Data Extraction", *Intl. J. of Adv. Comp. Eng and Net.*, v3, 71-74, 2015

**A Stroke Data Repository to Facilitate Big Data Research:
A Taiwan and NIH Collaborative Experience**

Yang C. Fann, Ph.D.

Director, IT and Bioinformatics Program,
National Institute of Neurological Disorders and Stroke,
National Institutes of Health, Bethesda, MD, USA

Recently, big data combined with machine learning (ML) and artificial Intelligence (AI) are dominating the field of data science research. It is believed that future data-driven biomedical discoveries and medical breakthroughs for better health outcomes can be substantially accelerated through ML/AI research, for example, precision medicine. In 2018, NIH has established a strategic plan for data science with commitments to FAIR principles, that is, making data Findable, Accessible, Interoperable, and Reusable to enable ML/AI research. With this forward thinking objective, NINDS has collaborated with Taiwan TSR (Taiwan Stroke Registry) to create a data repository for big data research including the creation of Stroke AI tools aiming to improve acute care. In this presentation, we will discuss the strategy and approaches in synergizing both NIH funded datasets and TSR data repository. The shared experience of this collaboration with examples of recent accomplishments will be presented.

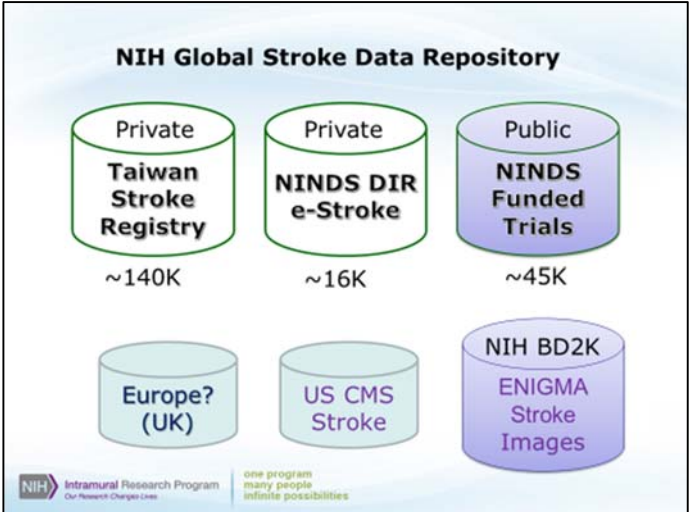
Presentation Slides



**A Stroke Data Repository to Facilitate Big Data Research:
A Taiwan and NIH Collaborative Experience**

Yang C. Fann, Ph.D.
Director, IT and Bioinformatics Program
NINDS/NIH/HHS

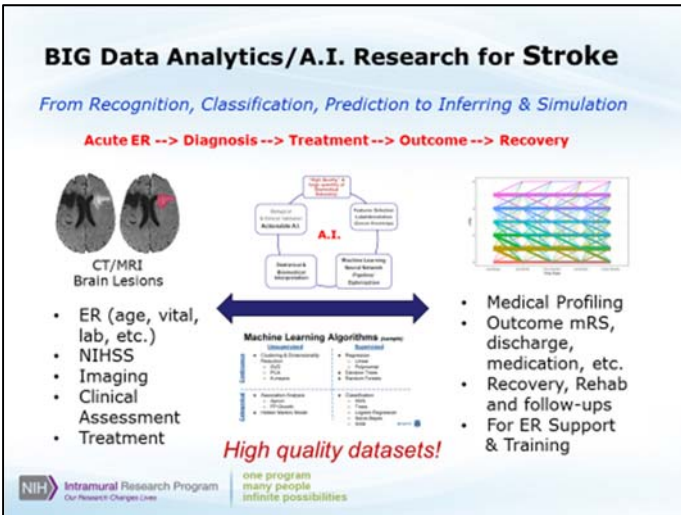
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Our Research Changes Lives



NIH Global Stroke Data Repository

- Private **Taiwan Stroke Registry** (~140K)
- Private **NINDS DIR e-Stroke** (~16K)
- Public **NINDS Funded Trials** (~45K)
- Europe? (UK)
- US CMS Stroke
- NIH BD2K **ENIGMA Stroke Images**

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Our Research Changes Lives



BIG Data Analytics/A.I. Research for Stroke
From Recognition, Classification, Prediction to Inferring & Simulation

Acute ER --> Diagnosis --> Treatment --> Outcome --> Recovery

CT/MRI Brain Lesions

- ER (age, vital, lab, etc.)
- NIHSS
- Imaging
- Clinical Assessment
- Treatment

A.I.

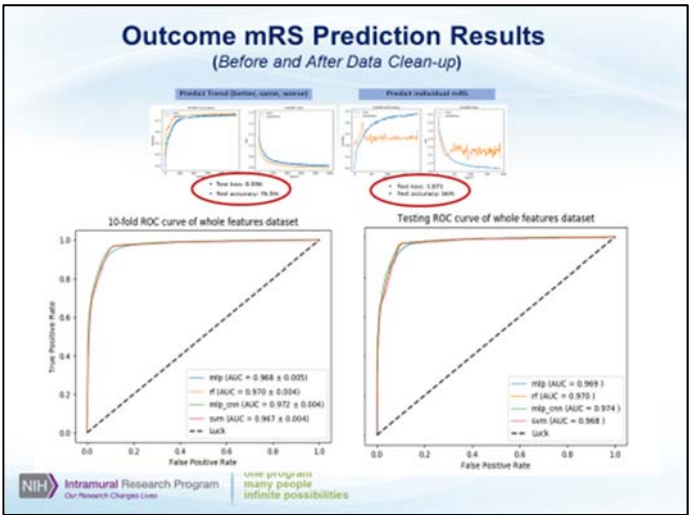
Machine Learning Algorithms

- Classification: Logistic Regression, SVM, Decision Tree, Random Forest, Gradient Boosting, Neural Networks
- Regression: Linear Regression, Ridge Regression, Lasso Regression, Elastic Net, Support Vector Regression, Neural Networks
- Clustering: K-Means, Hierarchical Clustering, DBSCAN
- Dimensionality Reduction: PCA, t-SNE, UMAP
- Association Rules: Apriori, FP-Growth
- Association Analysis: Lift, Leverage, Conviction, Interest, AllRules
- Association Metrics: Support, Confidence, Lift, Leverage, Conviction, Interest, AllRules

High quality datasets!

- Medical Profiling
- Outcome mRS, discharge, medication, etc.
- Recovery, Rehab and follow-ups
- For ER Support & Training

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Outcome mRS Prediction Results
(Before and After Data Clean-up)

10-fold ROC curve of whole features dataset

- mfp (AUC = 0.968 ± 0.001)
- rf (AUC = 0.970 ± 0.004)
- mfp_om (AUC = 0.972 ± 0.004)
- svm (AUC = 0.967 ± 0.004)
- luck

Testing ROC curve of whole features dataset

- mfp (AUC = 0.969)
- rf (AUC = 0.970)
- mfp_om (AUC = 0.974)
- svm (AUC = 0.968)
- luck

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Session II: Big Data



Chung Y. Hsu (許重義), MD, PhD

Chair Professor

China Medical University and Healthcare System

Taichung, Taiwan

Email: hsucy63141@gmail.com

hsuc@mail.cmuh.org.tw

hsuc@mail.cmu.edu.tw

Current Position:

Trustee, Board of Trustees, China Medical University and Healthcare System, Taichung, Taiwan (2014 -)

Trustee, Board of Trustees, Chinese Medical Advancement Foundation (2008 -)

Trustee, Board of Trustees, Brain Disease Prevention and Therapy Foundation (2012 -)

Trustee, Board of Trustees, Chang-Hai Tsai Education Foundation (2014 -)

Trustee, Board of Trustees, Tseng-Lien Lin Charity Foundation (2014 -)

Chair Professor, Graduate Institute of Clinical Medical Science, China Medical University (2008-)

Principal Investigator, Taiwan Stroke Registry (2006 -)

Principal Investigator, Taiwan Biobank - Stroke Biosignature Project (2012 -)

Principal Investigator, Ministry of Health Clinical Trial and Research Center of Excellence (2010 -)

Principal Investigator, National Research Program for Biopharmaceuticals – Taiwan Clinical Trial Consortium for Stroke (2013-)

Principal Investigator, SPAD, Pass, EXTEND International (Taiwan sites), ATACH-II (Taiwan sites), TASTE (Taiwan sites), STOP-AUST (Taiwan sites), PISA (under planning), STOP-MSU (under planning), DIRECT-SAFE (under planning)

Member, Editorial Board, Journal of Cerebral Blood Flow and Metabolism (1998 -)

Ambassador, Taiwan, Society for Clinical Research Sites (2016-)

Director, Office of Big Health Data Analytics, China Medical University Hospital (2010-)

Fellow, American Heart Association (1996-)

Member, Program Committee, World Stroke Organization (2014 -)

Who's Who in the World (1997 -)

Past Appointments:

Trustee, Board of Trustees, National Health Research Institute (2007-2019)

CEO, China Medical University Healthcare System, Taichung, Taiwan (2008 – 2014)

President, Taipei Medical University (2002 – 2008)

Director, Barnes-Jewish Hospital - Washington University Stroke Center (Ranked #1 in the US by Health Grade, 2000) and Elliott H. Stein Professor of Neurology, Washington University School of Medicine, St. Louis, MO (1993-2002)

Member, NIH-NICHD National Advisory Board on Medical Rehabilitation and Research (1997-2001)

Member, NIH-NINDS Neurological Disorder Program Project A Study Section (1988-1992).
Chair, 12 NIH-NINDS site visit teams or review panels, (1988-1997)
Chair, American Heart Association Brain Review Committee (1996-1997)
Chair, American Heart Association Bugher Foundation Stroke Awards Review Committee (1999 – 2001)
Member, NIH Clinical Neuroscience and Disease Study Section (2003 - 2005)
Member, Editorial Board, Stroke (1995 - 2010)
Member, Editorial Board, Journal of Neurotrauma (1991 – 2010)
Consultant, 16 pharmaceutical companies in the US, Europe and Japan (1992 -2002)
Member, Scientific Advisory Board, 6 biotech companies in the US (1992 -2002).
President, American Neurotrauma Society (1991-1992)
President, North America Taiwanese Professors' Association (1995-1996)
President, Taiwan Stroke Society (2008-2009)
President, Taiwan Neuroscience Society (2006-2007)

Honors:

Distinguished Alumnus Award, Chung-San Elementary School, Taipei
Outstanding Reviewer Award, Journal of Formosa Medical Association (2014)
National Honor of Panama for Exceptional Research Contributions to Neuroscience (2011)
NIH-NINDS Javits Neuroscience Investigator award (1991 – 1998)
Taiwanese Americans Outstanding Achievement Award (1997)
Bob and Vivian Smith Foundation Distinguished Research Award (1993-1994)
NIH-NINDS Teacher-Investigator Award (1983-1988)
Distinguished Leadership Award, Barnes-Jewish Hospital and Washington University School of Medicine (2000)
Distinguished Leadership, Dana Alliance for Brain Initiatives (2000)

Publications:

More than 300 papers in SCI journals including **New England Journal of Medicine, JAMA, Science, Nature Medicine** and others with more than 18,000 citations.

Education:

National Taiwan University School of Medicine (MD)
University of Virginia, USA (PhD in Pharmacology)

Beyond Multicenter Trial Results: Application of Big Health Databases to Establish Real-world Evidence

Chung Y. Hsu, MD, PhD

We have entered the Big Data Era with business operation, technology R&D and biomedical research applying big data bases within respective disciplines. Big health data has been evolving to become the foundation for future development of healthcare applying artificial intelligence (AI). Real-world Evidence derived from big health database will be the ultimate proof of evidence generated by multicenter clinical trial results. National Health Insurance (NHI) in Taiwan is a universal healthcare insurance started in 1995. NHI has been praised by world authorities including Prof. Paul Krugmen, the 2008 Nobel Prize-winning economist, to be among the best health insurance systems in the world. A unique strength of NHI is its systematic recording of healthcare data to build one of the largest big health database in the world which is a “gold mine” for conducting research based on big health databases. Searching PubMed for “Taiwan National Health Insurance” yielded 6,444 papers as of August 9, 2019. The achievements that have been made applying this unique big health database in clinical research and biotech R&D will be presented by demonstrating some of the published papers that have built the real world evidence to surpass evidence derived from multicenter clinical trials.

Real World Evidence

beyond Multicenter Clinical Trials

Advances in Healthcare **Applying Big Data Analytics**

Chung Y. Hsu, MD, PhD, FAHA, FAAN **Sample Paper #1**

JAMA | Original Investigation

Association of Varicose Veins With Incident Venous Thromboembolism and Peripheral Artery Disease

Shyue-Luen Chang, MD; Yau-Li Huang, MD; Mei-Ching Lee, MD; Sindy Hu, MD; Yen-Chang Hsiao, MD; Su-Wei Chang, PhD; Chese Jen Chang, PhD; Pei-Chun Chen, PhD

IMPORTANCE Varicose veins are common but rarely associated with serious health risks. Deep venous thrombosis (DVT), pulmonary embolism (PE), and peripheral artery disease (PAD) are also vascular diseases but associated with serious systemic effects. Little is known about the association between varicose veins and the incidence of other vascular diseases including DVT, PE, and PAD.

OBJECTIVE To investigate whether varicose veins are associated with an increased risk of DVT, PE, or PAD.

Support

CME

jama

MJ Group Health Database

Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi-Fong Wen, Jackson Pui Man Wong*, Ming-Kuang Tsai, Yi-Chen Yang, Ting-Tsun David Cheng, Wen-Chih Lee, Hsi-Ting Chao, Chien-Kang Tsao, Shou-Pao Tsai, Kijong Wu*

Summary
Background The health benefits of leisure-time physical activity are well known, but whether less exercise than the recommended 150 min a week can have life expectancy benefits is unclear. We assessed the health benefits of a range of volumes of physical activity in a Taiwanese population.

Methods In this prospective cohort study, 41617 individuals (199265 men and 216910 women) participated in a standard medical screening programme in Taiwan between 1996 and 2006, with an average follow-up of 1.05 years (SD 4.2). On the basis of the amount of weekly exercise indicated in a self-administered questionnaire, participants were placed into one of five categories of exercise volumes: inactive, or low, medium, high, or very high activity. We calculated hazard ratios (HR) for mortality risks for every group compared with the inactive group, and calculated life expectancy for every group.

Findings Compared with individuals in the inactive group, those in the low-volume activity group, who exercised for an average of 92 min per week (95% CI 71-112) or 15 min a day (SD 1.8), had a 14% reduced risk of all-cause mortality (0.86, 0.81-0.91), and had a 1 year longer life expectancy, every additional 15 min of daily exercise beyond the minimum amount of 15 min a day further reduced all-cause mortality by 4% (95% CI 2.5-7.0) and all-cancer mortality by 1% (0.3-4.5). These benefits were applicable to all age groups and both sexes, and to those with cardiovascular disease risk. Individuals who were inactive had a 17% (HR 1.17, 95% CI 1.09-1.24) increased risk of mortality compared with individuals in the low-volume group.

Interpretation 15 min a day or 90 min a week of moderate-intensity exercise might be of benefit, even for individuals at risk of cardiovascular disease.

Funding Taiwan Department of Health Clinical Trial and Research Center of Excellence and National Health Research Institutes.

"An epidemic of cardiovascular disease is just beginning in many countries that are ill prepared for what is to come."

Real World Evidence
beyond
Multicenter Clinical Trials

Advances in
Healthcare
**Applying Big Data
Analytics**

Sample Paper #2

The Lancet, Volume 378, Issue 9798, Pages 1244 - 1253, 1 October 2011

Real World Evidence

beyond
Multicenter Clinical Trials

Advances in Healthcare **Applying Big Data Analytics**

Taiwan Stroke Registry: Real World Practice Outcomes

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Learn and Live...

Sample Paper #3

Get With The Guidelines-Stroke Performance Indicators: Surveillance of Stroke Care in the Taiwan Stroke Registry. Get With The Guidelines-Stroke in Taiwan
 Fang-I Hsieh, Li-Ming Lien, Sien-Tsong Chen, Chya-Huey Bai, Mu-Chien Sun, Hung-Fin Tseng, Yu-Wei Chen, Chih-Hung Chen, Jiaun-Shing Jeng, Song-Yen Tsai, Huey-Juan Lira, Chuang-Hsin Wang, Lina, Yuh-Juei Kwan, L. O., Hsun-Jung Chen, Hsu-Chang, Chau, Ming-Liang Lai, Ruey-Tay Lira, Ming-Hui Sun, Bak-Sau Yip, Hung-Yi Chou, Chang Y. Hsu and the Taiwan Stroke Registry Investigators

Table 4. Outcomes based on Performance Indicators

	n	OR [I]	95% CI	P Value
Functional outcomes (RFS)* by LOS for 2 hours				
0-1 month post stroke	1249	0.30	0.27	0.0002
0-3 months post stroke	1045	0.47	0.32	0.0002
0-6 months post stroke	990	0.82	0.39	0.0009
Risk of cardiovascular events and death, 1 antithrombotic at discharge				
0-1 month post stroke	17952	0.19	0.16	<0.0001
0-3 months post stroke	16908	0.33	0.28	<0.0001
0-6 months post stroke	16163	0.41	0.26	0.047

Session II: Big Data



Tsutomu Nishimura, MPH, PhD

Associate Professor

Global Development Office, Institute for Advancement of
Clinical and Translational Science (iACT),
Kyoto University Hospital

Email: tnishimu@kuhp.kyoto-u.ac.jp

Profile

Dr. Tsutomu Nishimura is an associate professor at the Institute for Advancement of Clinical and Translational Science (iACT), Kyoto University Hospital. He graduated from the College of Medical Technology, Kyoto University, in 2004, from a master's course at the Kyoto University School of Public Health in 2006, and completed PhD coursework at the Graduate School of Medicine, Kyoto University, in 2010 before obtaining his PhD from there in 2011. Dr. Nishimura then worked as a project manager for clinical trials at the Translational Research Center for Medical Innovation (Kobe, Japan) from 2011 to 2018. He took up his current position at Kyoto University in 2018.

Specializations

1. Environmental medicine
2. Epidemiology
3. Design, management, and evaluation of clinical trials

Selected Publications

1. Nishimura T, Tada H, Fukushima M. Correlation between the Lunar Phase and Tail-Lifting Behavior of Lizards (*Pogona vitticeps*) Exposed to an Extremely Low-Frequency Electromagnetic Field. *Animals (Basel)*. 2019;9(5). E208.
2. Nishimura T, Tada H, Nakatani E, Matsuda K, Teramukai S, Fukushima M. Stronger geomagnetic fields may be a risk factor of male suicides. *Psychiatry Clin Neurosci*. 2014;68:404-9.
3. Tada H, Nishimura T, Nakatani E, Matsuda K, Teramukai S, Fukushima M. Association of geomagnetic disturbances and suicides in Japan, 1999-2010. *Environ Health Prev Med*. 2014;19:64-71.
4. Nishimura T, Tada H, Guo X, Murayama T, Teramukai S, Okano H, Yamada J, Mohri K, Fukushima M. A 1- μ T extremely low frequency electromagnetic field versus sham-control for mild to moderate hypertension: a double-blind, randomized study. *Hypertension Research*

2011; 34, 372–377.

5. Nishimura T, Okano H, Tada H, Nishimura E, Sugimoto K, Mohri K, Fukushima M. Lizards Respond to an Extremely Low-Frequency Electromagnetic Field. *Journal of Experimental Biology* 2010; 213: 1985-1990.

Abstract

The relationships between weather-related factors and disease are being established in the field of biometeorology. One example is how the German Meteorological Service provides health forecast information known as *Biowetter*, based on meteorological data. In addition to weather-related factors, we are focusing on space-related factors with regard to disease exacerbation and onset. First, we focused on suicide. Against the backdrop of reports on the relationship between geomagnetic disturbances and the number of suicides outside of Japan, we found the monthly mean geomagnetic disturbance index (K-index value) was associated with the monthly number of suicides among males in Japan. If this is a valid relation, stronger geomagnetic fields may affect the number of suicides. This is because stronger geomagnetic fields generally cause greater geomagnetic disturbances. We therefore investigated the relation between local geomagnetic field magnetic flux density and the standardized mortality ratios for suicide, by each prefecture in Japan. We found that stronger geomagnetism is associated with a higher standardized mortality ratio for suicides among males in Japan. Additionally, using health insurance data from Taiwan, we found there is a significant association between monthly geomagnetic disturbances and the number of suicides in both sexes.

Session III

Special Session for Cancer Translational Research

Moderator: (JP) Norihiro Sato, Hokkaido University

Session III: Special Session for Cancer Translational Research



Hiroshi Fukuhara, MD, PhD

Professor and Chairman

Department of Urology, Kyorin University School of Medicine

Email: hfukuhara-jua@umin.ac.jp

【Profile】

Education:

1989 – 1995 M.D., The University of Tokyo, Faculty of Medicine, Tokyo, Japan

1998 – 2002 M.D. Ph.D., The University of Tokyo, Graduate School of Medicine, Tokyo, Japan

Research:

1998 – 2001 National Cancer Center Research Institute, Tokyo, Japan

2001 – 2003 Massachusetts General Hospital, Harvard Medical School, Boston, US

Professional Experience:

2006 – 2014 Assistant Professor, Department of Urology,

2014 – 2018 Associate Professor, Department of Urology,

Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

2018 – present Professor and Chairman, Department of Urology,

Kyorin University School of Medicine, Tokyo, Japan

【Professional interests and specialties】

Specialty Board Certification: urological specialist

【Selected Publications】

1. Kuramochi M#, Fukuhara H#, Nobukuni T#, Kanbe T, Maruyama T, Ghosh HP, Pletcher M, Isomura M, Onizuka M, Kitamura T, Sekiya T, Reeves RH and Murakami Y. TSLC1 is a tumor suppressor gene in human non-small cell lung cancer. *Nature Genetics* 27: 427-430, 2001. (#equal contribution)
2. Fukuhara H, Martuza RL, Rabkin SD, Ito Y and Todo T. Oncolytic Herpes Simplex Virus Vector G47Δ in Combination with Androgen Ablation for the Treatment of Human Prostate Adenocarcinoma. *Clinical Cancer Research* 11: 7886-7890, 2005.
3. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. *Cancer Sci* 107: 1373-1379, 2016.
4. Taguchi S, Fukuhara H*, Todo T. Oncolytic virus therapy in Japan: progress in clinical trials and future perspectives. *Jpn J Clin Oncol*. 2019, in press.

【Abstract】

We report the findings of a phase I dose-escalating study of a third-generation, triple-mutated oncolytic herpes virus type 1 (HSV-1), G47 Δ , in patients with castration-resistant prostate cancer (CRPC). This is the first clinical trial in which oncolytic HSV-1 was used for the treatment of prostate cancer.

Oncolytic HSV-1 is an attractive therapeutic agent for treating cancer due to its capacity to selectively replicate in cancer cells, kill them, and spread their progeny to surrounding cancer cells. IMLYGIC™ (Talimogene laherparepvec), a second-generation oncolytic HSV-1, was approved as the first oncolytic virus drug in the United States in 2015. G47 Δ used in this study is a third-generation oncolytic HSV-1 that has triple mutations in the *gamma34.5*, *alpha47* and *ICP6* genes.

In this single-armed phase I study, patients with prostate cancer that had not received prostatectomy and recurred after hormonal therapy, with or without prior record of chemotherapy and with or without remote metastases, are included. The clinical-grade G47 Δ was manufactured at the GMP Vector Production Facility at the Institute of Medical Science, the University of Tokyo. The quality tests were performed extensively under GLP at four steps of manufacture. G47 Δ was injected directly into the prostate by a transrectal ultrasound-guided transperineal technique. The primary endpoint is to assess the safety of G47 Δ . A dose escalation was planned in 3 cohorts with 3 subjects per cohort.

The treatment has been well tolerated by the patients, and no severe adverse events attributable to G47 Δ have been observed. Some patients achieved a decreased PSA level for more than 50%. The current status and recent data of this clinical trial will be presented.

SessionIV

Cancer Translational Research

Moderator1: (JP) Toshirou Nishida, Japan national cancer center hospital
(TW) Andrew H.-J. Wang, Academia Sinica

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(TW) Andrew H.-J. Wang, Academia Sinica

Session IV: Cancer Translational Research

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【Abstract】

International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX study)

In general, clinical outcomes of surgery for malignant epithelial tumors are greatly influenced by quality of surgery, particularly that of lymph node (LN) dissection. In both complete mesocolic excision (CME) and Japanese D3 dissection, surgical procedures for colon cancer increasingly adopted in the West and East, radical LN dissection including removal of LNs located at the root of the major feeding arteries (main nodes) is employed. However, surgical benefit of removing main nodes *en bloc* has not fully been confirmed and we have to identify a subgroup of colon cancer patients who could benefit from radical LN dissection. In addition, we have no robust evidence to support which is appropriate in length of bowel resection, Western-type wide bowel resection or the Japanese 10 cm-rules. The optimal extent of bowel resection is closely associated with how we define “regional” pericolic LNs located along the bowel which should be removed because of the risk of metastasis, but there is no consensus for “regional” LNs in the pericolic region.

T-REX study is a prospective international observational cohort study conducted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), involving 34 institutions not only in Japan, but also in Korea, Russia, Lithuania, Germany, Taiwan, and UK. This study aims to clarify the actual distribution of metastatic LNs in colon cancer and provides reliable evidence both of the appropriate extent of central LN dissection and of optimal length of bowel resection in colon cancer surgery. In addition, high-resolution photographs of fresh resected specimens taken with a digital color camera are analyzed by Prof Philip Quirke’s team at Leeds University. This sub-study allows us to determine the macroscopic grading the quality of the mesocolic dissection (Lancet Oncol 2008; JCO 2010/2012). A total of 3696 colon cancer patients have been enrolled between January 2015 and December 2018, and we are now in the process of data cleaning. T-REX study is expected to determine the area of LNs to be regarded as “regional” in colon cancer and to provide method of quality control of colon cancer surgery.



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Profile

Dr. Jin-Tung Liang currently serves as President of Taiwan Robotic Surgery Association (TRSA) and Taiwan Society of Coloproctology. After obtaining the M.D degree from Medical College of National Taiwan University in 1987, he served 2-year military service, and then completed the 5-year residency of general surgery and has been the attending surgeon in the division of Colorectal Surgery in National Taiwan University Hospital since 1994. Dr. Liang has ample experiences in his professional field of colorectal surgery and had published more than 100 research articles. The main theme of his academic achievements has been on the translational research of colorectal cancer. He develop many surgical innovations for the clinical treatment of Taiwanese patients, such as the clarification of molecular biologic characteristics of Taiwanese colorectal cancer, and one of the pioneers of laparoscopic and robotic surgery for colorectal cancer in Taiwan. Also, he is an active council member both in domestic and international associations, such as Formosan Association of Surgery and American Society of Colorectal Surgery. Currently, he is the chief of colorectal division and the full professor of department of surgery, Medical College of National Taiwan University. Dr. Liang has been the associate editor of Korean Society of Coloproctology since 2010. Remarkably, in 2014, he took over the position of editor-in-chief of Asian Journal of Surgery (impact factor: 1.560), which is the only one SCI journal in the field of surgery in Taiwan. Due to his long endeavor in the surgical innovation, he received the 11th National Innovation Award in the Clinical Research Category by the Institute for Biotechnology and Medicine Industry in 2015.

Selected Publications

1. **Liang JT**, Lai HS, Huang J, Sun CT. Long-term oncologic results of laparoscopic D3 lymphadenectomy with complete mesocolic excision for right-sided colon cancer with clinically positive lymph nodes. *Surg Endosc*. 2015 Aug 29(8):2394-401
2. Lin BR, Lin YL, Lai HS, Lee PH, Chang KJ, **Liang JT(corresponding author)** Overall Survival of Stage III Colon Cancer with Only One Lymph Node Metastasis Is Independently Predicted by Preoperative Carcinoembryonic Antigen Level and Lymph Node Sampling Status. *PLoS One*. 2015 Sep 18;10(9):e0137053.
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 14. Chang LC, Tu CH, Lin BR, Shun CT, Hsu WF, **Liang JT**, Wang HP, Wu MS, Chiu HM. Adjunctive use of chromoendoscopy may improve the diagnostic performance of narrow-band imaging for small sessile serrated adenoma/polyp. *J Gastroenterol Hepatol*. 2017 Jul 7. doi: 10.1111/jgh.13863.
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 30. Chen TC, Liang JT. Robotic Radical Surgery in the Multidisciplinary Approach for the Treatment of Locally Advanced T4 Rectosigmoid Colon Cancer. *Dis Colon Rectum.* 2019 Jan; 62(1):121-122.
 31. Liang JT, Chen TC. Robotic Top-Down Intersphincteric Resection with IPAA for Familial Adenomatous Polyposis with Distal Rectal Cancer. *Dis Colon Rectum.* 2019 (in press)



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Education

Kaohsiung Medical University, Post Baccalaureate Medicine 2003/09-2008/06
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Postgraduate Training

Surgical Resident, Far Eastern Memorial Hospital 2008/07-2010/06
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Professional Experience

Attending physician, Division of Colorectal Surgery, Department of Surgery, National Taiwan University Hospital, Hsinchu Branch 2014/08~2018/07
Attending physician, Division of Colorectal Surgery, Department of Surgery, National Taiwan University Hospital, Taipei 2018/08~present

Board Certification

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Society of Colon and Rectal Surgeons, Taiwan.
Taiwan Surgical Society of Gastroenterology
Taiwan Association for Endoscopic Surgery

Professional societies

Taiwan Surgical Association
Society of Colon and Rectal Surgeons, Taiwan.
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Taiwan Society of Coloproctology (Secretary General, 2016~present)
Taiwan Robotic Surgery Association
Taiwan Peritoneal Oncological Association (Council Member, 2019~present)

Publications

1. Chen TC, Chang CH, Chou TH, Hung JS, Huang J, Lin BR, Liang JT. Prognosis of T0 and T1 Colorectal Cancer Following Surgical Resection. J Soc Colon Rectal Surgeon (Taiwan) December 2014, 134-140
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5. Chen TZ, Hung JS, Lin BR, Huang John, Liang JT. Long-term follow-up for patients with colonic perforation due to colonoscopy: From clinical and medicolegal viewpoints. *Formosan Journal of Surgery*. 2017;50:195-199.
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14. Chen TC, Liang JT. Chap 29 Perianal abscess and fistula. *Clinical Surgery Core Course 100*.
15. Liang JT, Huang J, Chen TC, Hung JS. The Toldt fascia: A historic review and surgical implications in complete mesocolic excision for colon cancer. *Asian J Surg*. 2019;42:1-5.
16. Liang JT, Huang J, Chen TC. Standardize the Surgical Technique and Clarify the Relevant Anatomic Concept for Complete Mobilization of Colonic Splenic Flexure Using da Vinci Xi® Robotic System. *World J Surg*. 2019;43(4):1129-1136.

Long-Term Oncologic Results of Laparoscopic D3 Lymphadenectomy with Complete Mesocolic Excision for Right-Sided Colon Cancer with Clinically Positive Lymph Nodes

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Complete mesocolic excision (CME)

Background/Aim: To assess surgical outcomes of patients undergoing D3 lymph node dissection and complete mesocolic excision for the treatment of right-sided colon cancer in the context that both procedures were performed laparoscopically.

Methods: 244 **consecutive** patients with clinically staged III right-sided colon cancer were recruited to undergo the laparoscopic D3 lymph node dissection with complete mesocolic excision. Postoperatively, the patients were stratified as N0, N1, N2 and N3 groups according to the level of lymph node metastasis, prospectively followed up for more than 5 years, and compared.

Results: The 5-year cumulative recurrence rate and the estimated time-to-recurrence [mean (95% confidence interval)] was 16.6% (n=7/42), 113.8 (101.4-126.2) months in N0 group; 21.3% (n=17/80), 108.9 (99.1-118.7) months in N1 group; 43.2% (n=32/74), 85.4 (73.0-97.8) months in N2 group; and 52.0% (n=25/48), 65.2 (49.0-81.4) months in N3 group. When N1 and N2 groups of patients were lumped together, and compared with patients with N2 or N3 metastasis, we found that the latter were with a significantly higher recurrence rate ($p < 0.0001$). D3 lymph node dissection with complete mesocolic excision could assure the harvest of sufficient number ($n = 34.4 \pm 8.4$) of lymph nodes for precise pathologic cancer staging. Skip lymph node metastasis were detected in 19.8% (n=40/202) of patients and such surgical procedures facilitated up-staging in 4.5% (n=11/244) of patients.

Conclusion: The present study encourages the dissemination of such concepts to surgical oncologists dealing with colorectal cancer through didactic education and international consensus meeting is therefore mandatory to optimize the surgery of colon cancer.

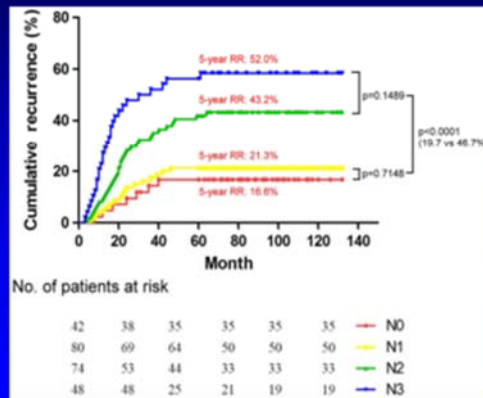
Key word: laparoscopic surgery, N3 lymph-node, D3 lymphadenectomy, colon cancer, complete mesocolic excision

Long-Term Oncologic Results of Laparoscopic D3 Lymphadenectomy with Complete Mesocolic Excision for Right-Sided Colon Cancer with Clinically Positive Lymph Nodes



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5-Year survival rate is enhanced through MIS CME



NTUH Experiences:

The excellent stability and dexterity provided by Da Vinci robotic system are unique in performing the following procedures:

- 1. Finding out the precise dissection plane for CME or TME
- 2. Low-lying rectal cancer in deep, obese, narrow pelvis
- 3. Extensive lymph node dissection for advanced colorectal cancers
- 4. Metastasectomy for the isolated recurrent lesion from colorectal cancer.

Session IV: Cancer Translational Research



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【Profile】

Dr. Masahiro Takada is Assistant Professor at the Department of Breast Surgery, Kyoto University Hospital. He graduated from the School of Medicine, Hokkaido University in 2000, and obtained his PhD from Graduate School of Medicine, Kyoto University in 2012. He worked at the Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo, Japan) from 2001 to 2006 for residency training and fellowship. He joined Kyoto University Hospital in 2007 and was promoted to assistant professor in 2014. The doctoral training program he received is “Raising Proficient Oncologists,” run by the Japanese Ministry of Education, Culture, Sports, Science and Technology. He is a certified trainer of the Japan Breast Cancer Society since 2018 and recognized by the Japan Surgical Society as certified trainer in 2019. In addition to clinic practice and teaching, he has published 34 peer-reviewed papers in breast cancer field.

【Professional interests and specialties】

1. Breast Surgery
2. Breast Cancer Research

【Selected Publications】

1. Takada M, Toi M. Cryosurgery for primary breast cancers, its biological impact, and clinical outcomes. *Int J Clin Oncol*. 2019 Apr 13. doi: 10.1007/s10147-019-01448-4. [Epub ahead of print]
2. Takada M, Sugimoto M, Masuda N, Iwata H, Kuroi K, Yamashiro H, Ohno S, Ishiguro H, Inamoto T, Toi M. Prediction of postoperative disease-free survival and brain metastasis for HER2-positive breast cancer patients treated with neoadjuvant chemotherapy plus trastuzumab using a machine learning algorithm. *Breast Cancer Res Treat*. 2018 Dec;172(3):611-618.
3. Sagara Y, Takada M, Ohi Y, Ohtani S, Kurozumi S, Inoue K, Kosaka Y, Hattori M, Yamashita T, Takao S, Sato N, Iwata H, Kurosumi M, Toi M. Effectiveness of neo-adjuvant

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12. Takada M, Terunuma H, Deng X, Dewan MZ, Saji S, Kuroi K, Yamamoto N, Toi M: Refractory lung metastasis from breast cancer treated with multidisciplinary therapy including an immunological approach. *Breast Cancer* 18:64-7, 2011
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【Abstract】

Ductal carcinoma in situ (DCIS) is a diverse group of diseases ranging from those that are immutable for several decades with no impact on prognosis to those that progress to invasive cancer. Overdiagnosis and overtreatment have proven problematic for diseases that are considered not to affect prognosis. However, studies on the natural history and biology of DCIS and high-risk lesions, such as atypical ductal hyperplasia, and lobular carcinoma in situ, are still insufficient. In addition, diagnostic imaging and histopathological diagnosis of DCIS and high-risk lesions require skilled techniques; however, evaluation has not been sufficiently made on the accuracy of these diagnoses in clinical practice.

Therefore, we plan to build a multi-center registry of DCIS and high-risk lesions to understand the current accuracy of diagnostic imaging and histopathological diagnosis, and to construct clinical tools which improve diagnostic accuracy of the disease, and to develop a treatment algorithm which reduces overtreatment. We plan to integrate information on clinical, pathology, diagnostic imaging, and molecular diagnosis based on the registry data. It is expected that this will improve the diagnostic accuracy for DCIS and high-risk lesions and optimize the management.



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Profile

After completing clinical training as a medical oncologist at National Taiwan University Hospital (NTUH), I participated in the radiation oncology resident training at NTUH. My research interests focus on clinical trial and translational research for lymphoma, breast cancer, and radiation oncology. I have demonstrated that expression of cytotoxin-associated gene A (CagA) and CagA-signaling molecules is associated with *H. pylori* dependence of gastric lymphoma and have received “Dr. Chien-Tien Hsu’s Outstanding Cancer Research Award” from Taiwan Oncology Society in 2010. I was an invited speaker in the education session of 2013 American Society of Hematology (ASH) Annual Meeting. The session was entitled “*Helicobacter pylori* and MALT: what is new?”

In addition, my researches have demonstrated that polymorphisms of MAP3K1 and CYP19 are associated with the prognosis of hormone receptor-positive early-stage breast cancer, and expression of MAP3K1 correlates with local recurrence and disease-free survival in early-stage breast cancer and in breast ductal carcinoma in situ.

Professional interests and specialties

1. Radiation Oncology (Breast Cancer)
2. Lymphoma

Selected Publications

1. Kuo SH, Wu MS, Yeh KH, Lin CW, Hsu PN, Chen LT, Cheng AL. Novel Insights of Lymphomagenesis of *Helicobacter pylori*-Dependent Gastric Mucosa-Associated Lymphoid Tissue Lymphoma. *Cancers (Basel)*. 2019;11(4). pii: E547.
2. Kuo SH, Lo C, Chen YH, Lien HC, Kuo WH, Wang MY, Lee YH, Huang CS. Prognostic Significance of Clinicopathologic Features in Patients With Breast Ductal Carcinoma-in-Situ Who Received Breast-Conserving Surgery. *Clin Breast Cancer*. 2018;18(6):441-450.
3. Lai SF, Chen YH, Liang TH, Hsu CY, Lien HC, Lu YS, Huang CS, Kuo SH*. The breast graded prognostic assessment is associated with the survival outcomes in breast cancer patients receiving whole brain re-irradiation. *J Neurooncol*. 2018; 138(3):637-647
4. Kuo SH, Yang SY, You SL, et al. Polymorphisms of *ESR1*, *UGT1A1*, *HCN1*, *MAP3K1* and *CYP2B6* are associated with the prognosis of hormone receptor-positive early breast cancer. *Oncotarget*. 2017 Mar 28;8(13):20925-20938
5. Lai SF, Chen YH, Kuo WH, Lien HC, Wang MY, Lu YS, Lo C, Kuo SH*, Cheng AL, Huang CS*. Locoregional recurrence risk for postmastectomy breast cancer patients with T1-2 and one to three positive lymph nodes receiving modern systemic treatment without radiotherapy. *Ann Surg Oncol*. 2016 Nov;23(12):3860-3869.

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 7. Kuo SH, Tasi HJ, Lin CW, et al. B cell-activating factor signaling pathway is associated with *H. pylori* independence in gastric MALT lymphoma without t(11;18)(q21;q21). *J Pathol*. 2017 Feb;241(3):420-433
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Session IV: Cancer Translational Research

Radiotherapy Versus Low-Dose Tamoxifen Following Breast Conserving Surgery for Low-Risk and Estrogen Receptor-Positive Ductal Carcinoma in Situ of Breast: An International Open-Label Randomized Non-Inferiority Trial (TBCC and Japan ARO-DCIS Trial)

Sung-Hsin Kuo, Yasuaki Sagara, Masakazu Toi, and Chiun-Sheng Huang

Although the results obtained from Eastern Cooperative Oncology Group (ECOG) E5194 and *Radiation Therapy Oncology Group (RTOG) 9804* trial demonstrated that the 7-year ipsilateral breast tumor recurrence (IBTR) ranged from 5.6% to 10.5% for women with low-risk characteristics of ductal carcinoma in situ (DCIS) who underwent breast conserving surgery (BCS) alone without radiotherapy (RT), the aforementioned two studies included a proportional of patients who had young age and negative estrogen receptor (ER) status tumor. Our studies revealed that age <40 years and ER-negative status in tumor were independent prognostic factors for recurrence of breast DCIS irrespective of tumor characteristics. The UK/ANZ randomized trial demonstrated that a benefit of tamoxifen in terms of reducing the IBTR is observed in the BCS alone group but not found in the BCS plus RT group. A recent randomized trial showed that low-dose tamoxifen (5 mg QD) for 3 years significantly decrease local recurrence in patients with DCIS or other forms of intraepithelial neoplasia by 52% when compared with placebo arm after a median follow-up of 5.1 years. However, the effect of the administration of low-dose tamoxifen is similar to the RT effect in terms of reducing IBTR for women with low-risk DCIS remains unclear.

Throughout the discussion with the detailed criteria of low-risk characteristics of breast DCIS in the Taiwan Breast Cancer Consortium (TBCC) & Japan Academic Research Organization (ARO) DCIS trial meeting, we have designed a randomized non-inferiority trial to assess whether the effect of administration of tamoxifen (5 mg) for 5 years following BCS is not inferior in terms of reducing tumor recurrence when comparing RT (in terms of 50 Gy in 25 fractions or 40.05 Gy in 15 fractions) following BCS for patients who had age ≥ 40 years, low risks of *BRCA1* or *BRCA2* (Manchester Score <10), low-risk clinicopathological features (mammographically detected low- or intermediate-grade without comedo necrosis, measuring less than 2.5 cm with margins ≥ 3 mm), and positive-ER status of breast DCIS.

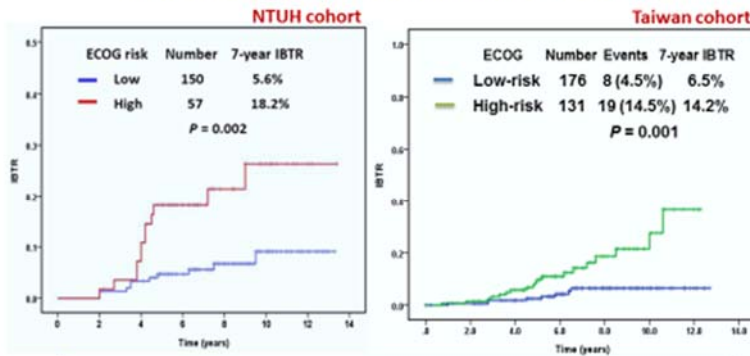
The primary end point of this study was breast tumor recurrence (included ipsilateral, regional, contralateral, and distant recurrence [DCIS or invasive cancer event]). The secondary endpoints were overall survival, and adverse effects of radiotherapy and tamoxifen. We estimate that 405 patients will be randomized to tamoxifen arm and 405 patients will be randomized to RT arm (margin, tumor recurrence difference, 5%; 90% β -power with a α type I error of 5%). We expect that the administration of low-dose tamoxifen is not inferior to the prescription of RT in terms of reducing tumor recurrence for women with low-risk characteristics of DCIS. This study will provide a treatment optional, low-dose tamoxifen, for women with low-risk breast DCIS to avoid potential potential toxicities from adjuvant RT.

Radiotherapy versus Low-Dose Tamoxifen Following Breast Conserving Surgery for Low-Risk and Estrogen Receptor-Positive Ductal Carcinoma in Situ of Breast: an international open-label randomized non-inferiority trial (TBCC-ARO DCIS Trial)

ClinicalTrials.gov Identifier: NCT04046159

Sung-Hsin Kuo, Yasuaki Sagara, Masakazu Toi, and
Chiun-Sheng Huang

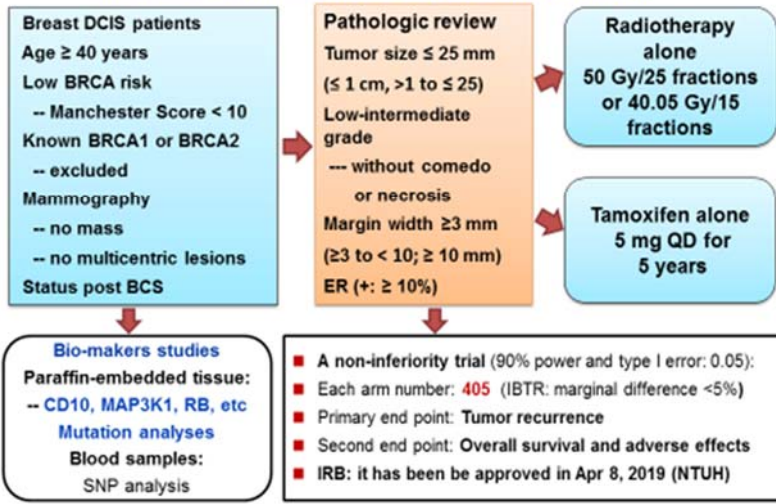
Low-risk ECOG criteria is significantly associated with the lower ipsilateral breast tumor recurrence (IBTR) in patients with breast DCIS (BCS alone, no radiotherapy)



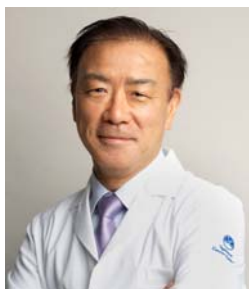
Low-risk criteria (ECOG):
Size ≤ 2.5 cm, low to intermediate risk (without comedo necrosis), and surgical margin ≥ 3 mm

Kuo SH, and Huang CS. Clin Breast Cancer. 2018 Dec;18(6):441-450.
Kuo SH, Cheng Skye HC, Tseng LM, Chang YC, Ou-Yang F, Kuo YL, Chang YZ, Yeh HT, Hsieh CM, Yeh MD, Chen HM, Chang WW, Chen ST, Huang CS. 2019 ESTRO Meeting

Radiotherapy versus Low-Dose Tamoxifen Following Breast Conserving Surgery for Low-Risk and Estrogen Receptor-Positive Ductal Carcinoma in Situ of Breast: an international open-label randomized non-inferiority trial (TBCC-ARO DCIS Trial)



Session IV: Cancer Translational Research



Toshirou Nishida, MD, PhD, FACS

Director,
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【Profile】

T. Nishida graduated from Osaka University Graduate School of Medicine, and had residency of general surgery in Osaka University Hospital and affiliated hospitals. He took postdoctoral fellowship in Tufts University, Boston.

He is a surgical oncologist expertized in gastrointestinal cancer, including gastric cancer and GIST.

In the clinical practice, he works as a surgeon of the Department of Gastric Surgery of NCCH. He is conducting several clinical studies and some basic as well as translational researches investigating the molecular mechanisms of gastrointestinal cancer with human samples. His research interests include elucidation of molecular mechanisms of carcinogenesis and cancer cell progression, and development of targeting therapy for sarcomas as well as gastrointestinal cancer. He has published more than 200 original reports in the major journals including Nat. Genet, Science, PNAS, Lancet, JCO and Gastroenterology and more than 30 review papers. At the same time, he devotes considerable effort to manage and organize the hospital as the director of the National Cancer Center Hospital.

【Professional interests and specialties】

1. Specialties: My specialty in clinical practice is gastrointestinal surgery including laparoscopic as well as open surgery for gastric cancer as well as GIST. I have been conducting and involved in several international clinical studies.
2. Interests: molecular mechanisms of GI cancer, and development molecularly targeting therapy of sarcomas as well as gastrointestinal cancer.

【Selected Publications】

1. Nishida T, Sakai Y, et al. Adherence to the guidelines and the pathological diagnosis of high-risk gastrointestinal stromal tumors in the real world. **Gastric Cancer**. 2019 Apr 30. doi: 10.1007/s10120-019-00966-4
2. Nishida T, Cho H, et al. Clinicopathological features and prognosis of primary GISTs with tumor rupture in the real world. **Ann Surg Oncol** 2019;26(3):829-835.
3. Nishida T, Hølmekjær T, Raut CP, Rutkowski P. Defining Tumor Rupture in Gastrointestinal Stromal Tumor. **Ann Surg Oncol**. 2019 Mar 13. doi: 10.1245/s10434-019-07297-9.
4. Kurokawa Y, Yang HK, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. **Br J Cancer**. 2017;117(1):25-32.

【Title】

Rare Cancer Registry and ReGISTry NETwork in Asia

【Abstract】

Patients with rare cancer defined as its incidence less than 60/million/year has several

challenges including delay in diagnosis and lack of treatment, and as a results, their prognosis is generally poorer than those with common cancer. Although international clinical trials are common in sponsor-initiated trials (SIT) in these days, they are infrequent in academic- and investigator-initiated trials (IIT), especially in Asia. International academic network and collaboration in IITs are required for medical development for rare cancer and pediatric cancer in which pharmaceutical companies may have little interest.

Our National Cancer Center Hospital is recently designated as the Core Clinical Research Hospital, Global Clinical Trials Core Center, and Central Organization for Rare Cancer in Japan. To clarify clinical, pathological, and genetic features of rare cancer and to facilitate medical development for patients with rare cancer, we are conducting the Masterkey project consisting of the registry study and sub-studies with basket and umbrella trials. In the sub-study part, several biomarker-based IITs or SITs are conducting and planned. The project is collaborated with several academic institutes, pharmaceutical companies and with Rare Cancers Japan, a patient advocacy group.

Asia may have a little ethnic difference; there are Asia-specific cancers; and short distance among countries; these factors may facilitate collaboration in clinical studies as well as registry studies in Asia. However, international collaboration in Asia have challenges in different regulations, different health insurance system, different requirements for compensation/indemnity, lack of support systems and funding for clinical trials, various standard therapy in each country, and different languages, as well. Thus, we are constructing Asian disease-specific registry network in addition to the above-mentioned project. This disease-specific registry consists from retrospective as well as prospective registry studies of GIST and NET in Japan, Korea, Taiwan and China. Particularly, between Japan and Taiwan, we are going to collaborate in epidemiological studies and retrospective as well as prospective GIST registry as a model of rare cancer registry collaboration.



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Profile

Ph.D. in Biostatistics, School of Public Health, University of North Carolina at Chapel Hill, US

2013/07~2019/07 Professor, School of Pharmacy, Kaohsiung Medical University (KMU), Taiwan

2004/12~2019/07 Director, Division of Medical Statistics and Bioinformatics, Department of Medical Research, KMU Hospital

2014/01~2019/07 Director, Medical Informatics and Statistics Center, Office of Research and Development, KMU

2014/07~2019/07 Director, Health and Welfare Data Science Center KMU Research Sub-Center, KMU

Professor Yi-Hsin Yang, also known as Connie Yang, has worked in the field of oral oncology and oral public health since 1996 as a faculty in the College of Dental Medicine, Kaohsiung Medical University. She had conducted several population-based studies in Taiwan on betel quid usage and prevalence of oral cancer/oral potentially malignant disorders (OPMD). She joined the faculty of College of Pharmacy in August 2011. Since then, she has been actively involved in the field of pharmacoepidemiology. Her research has focused on health related database analysis. She published several articles in chemoprevention agents for cancers as well as comparative effectiveness on cancer treatment modalities.

She has been devoted to promote research on real-world data (RWD) and real-world evidence (RWE) through the use of health administrative database and government database (particularly, the National Health Insurance Research Database, Cancer Registry Database, Cancer Screening Database, National Health Interview Survey, etc.). Her focus includes analysis methodology and clinical research using health database. While maximize data impact has become an important theme of current cancer control program, she serves as an expert in several Cancer Control related committees in the Ministry of Health and Welfare.

Professional interests and specialties

1. Maximize impact of real-world data in enhancing cancer control strategies,
2. Improve methodology to provide sufficient evidence for effectiveness and safety of cancer treatments,
3. Collaborate with multidisciplinary experts to integrate feasible clinical informatics for cancer patient care systems.

Selected Publications

First or corresponding authors since 2010

1. Ho PS, Wang WC, Huang YT, Yang YH: Finding an oral potentially malignant disorder in screening program is related to early diagnosis of oral cavity cancer - Experience from real world evidence. *Oral Oncol* 2019, 89:107-114.
2. Wu PC, Chen CT, Poon YC, Yang YH: Reply. *Ophthalmology* 2018, 125(11):e78.

3. Kuo HC, Wang RH, Wang JC, Yang YH: Assessing a conceptual model with both oral health and health related quality of life in community-dwelling elders. *Arch Gerontol Geriatr* 2018, 79:27-31.
4. Wu PC, Chen CT, Lin KK, Sun CC, Kuo CN, Huang HM, Poon YC, Yang ML, Chen CY, Huang JC, Wu PC, Yang IH, Yu HJ, Fang PC, Tsai CL, Chiou ST, Yang YH: Myopia Prevention and Outdoor Light Intensity in a School-Based Cluster Randomized Trial. *Ophthalmology* 2018, 125(8):1239-1250.
5. Ou YJ, Chiu HF, Wong YH, Yang CC, Yang YH: Bisphosphonate use and the risk of breast cancer: a meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf* 2017, 26(10):1286-1295.
6. Chiang WF, Yang YH: The impact of comorbidities on the management and prognosis of oropharyngeal and hypopharyngeal cancer patients in Taiwan. *Translational Research in Oral Oncology* 2017, 2:2057178X1772543.
7. Chen SC, Lee MY, Huang JC, Mai HC, Kuo PL, Chang JM, Chen HC, Yang YH: Association of diabetes mellitus with decline in ankle-brachial index among patients on hemodialysis: A 6-year follow-up study. *PLoS One* 2017, 12(4):e0175363.
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10. Ou YJ, Chiu HF, Wong YH, Yang YH: Bisphosphonate use and the risk of endometrial cancer: a meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf* 2016, 25(10):1107-1115.
11. Huang RY, Hsieh KP, Huang WW, Yang YH: Use of lithium and cancer risk in patients with bipolar disorder: population-based cohort study. *Br J Psychiatry* 2016, 209(5):393-399.
12. Hsieh KP, Chen LC, Cheung KL, Yang YH: Risks of nonadherence to hormone therapy in Asian women with breast cancer. *Kaohsiung J Med Sci* 2015, 31(6):328-334.
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14. Wu PC, Yang YH: Author reply: To PMID 23462271. *Ophthalmology* 2014, 121(4):e20-21.
15. Lin HS, Lin JR, Hu SW, Kuo HC, Yang YH: Association of dietary calcium, phosphorus, and magnesium intake with caries status among schoolchildren. *Kaohsiung J Med Sci* 2014, 30(4):206-212.
16. Hsieh KP, Chen LC, Cheung KL, Chang CS, Yang YH: Interruption and non-adherence to long-term adjuvant hormone therapy is associated with adverse survival outcome of breast cancer women--an Asian population-based study. *PLoS One* 2014, 9(2):e87027.
17. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK: Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology* 2013, 120(5):1080-1085.
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health-related quality of life with patients' satisfaction of new complete dentures. *Qual Life Res* 2013, 22(7):1665-1674.

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27. Kuo HC, Chen JH, Wu JH, Chou TM, Yang YH: Application of the Oral Health Impact Profile (OHIP) among Taiwanese elderly. *Qual Life Res* 2011, 20(10):1707-1713.
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Testing the Hypothesis of Reducing Cancer Risk with GSK-3 Inhibitor Using Taiwan National Health Insurance Database

Yi-Hsin Yang

National Institute of Cancer Research, National Health Research Institutes, Taiwan

Recent development in real-world data analysis has been widely investigated in many applications. In fact, by use of the population-based claims and registries database, one can further explore the possibility of testing hypotheses on potential targets for chemoprevention.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase involved in multiple cellular processes. Because of its multiple functions, GSK-3 plays important roles in many human disorders such as cancer. Consequently, GSK-3 inhibitors are speculated to be potential agents for treatment. The role of GSK-3 in cancer development remains complex and controversial. GSK-3 may play a positive role in cell proliferation and its aberrant expression as a tumor promoter. However, GSK-3 may also be a tumor suppressor, which can suppress the Wnt/b-catenin pathway by phosphorylating b-catenin. Lithium, discovered as the first inhibitor of GSK-3 in 1996, is primarily used for bipolar disorder and as augmentation therapy for refractory depression. Lithium is a mood stabilizer for the treatment of bipolar disorder, and provides several benefits: to prevent both manic and depressive episodes.

We design a pharmacoepidemiological study to investigate the association between lithium and cancer risk in patients with bipolar disorder by using the National Health Insurance Database in Taiwan. Our findings imply that lithium usage is associated with a lower incidence of overall cancer risk in patients with bipolar disorder. There is also a dose–response relationship for a higher cumulative dose associated with significant risk reduction in overall cancer risk. Our real-world data analysis platform can be further extended to a variety of potential targets on cancer chemoprevention.

Closing Remarks

Akira Myoui, Osaka University
Andrew H.-J. Wang, Academia Sinica

Closing Remarks



Akira Myoui, MD, PhD

Director

Medical Center for Translational Research, Department of
Innovation

Osaka University Hospital

【Profile】

Akira Myoui, MD, PhD graduated from Osaka University Medical School in 1986. After residency in orthopedics department of affiliated hospitals, he engaged in basic research on musculoskeletal tumor pathology at Osaka University Graduate School of Medicine, and molecular and cellular biology of bone at University of Texas at San Antonio. Then, he was promoted as an assistant professor at the Department of Orthopedics, Osaka University and further researched on bone substitute materials, bone cell biology and tissue engineering until 2006, and finally joined Medical center for Translational Research to work on the promotion of clinical translation of excellent basic biomedical discovery from Osaka University and other academic sectors.

In 2015, he was awarded Economy, Trade and Industry Minister's Prize for the contributors in Industry-Academia-Public Collaboration through the development of functional artificial bone.

Closing Remarks



Andrew H.-J. Wang (王惠鈞), PhD.

Distinguished Visiting Chair, Academia Sinica

Acting CEO, National Biotechnology Research Park

President, IUBMB

Email: ahjwang@gate.sinica.edu.tw

Profile

Dr. Wang, an eminent structural biologist, discovered Z-DNA, analyzed drug-DNA interactions and novel enzymes, publishing more than 450 refereed papers and 15 patents. In Taiwan, he educated/trained more than 100 students, postdocs and assistants; pioneered synchrotron bio-crystallography, founded scientific societies, ran national research programs, and well respected internationally (as FAOBMB and IUBMB presidents).

Professional interests and specialties

Structural proteomics, drug discovery, synchrotron crystallography, structure-function relationship of enzymes and DNA

Research/Professional Career:

- 2018: 2018 National Taiwan University Distinguished Alumnus
- 2017-present: Acting CEO, National Biotechnology Research Park
- 2017: Presidential Science Prize of Taiwan (Life Science)
- 2016-present: Distinguished Visiting Chair, Institute of Biological Chemistry, Academia Sinica
- 2015-: President-elect (-2018), President (2018-2021), Past-President (2021-2024), International Union of Biochemistry and Molecular Biology (IUBMB)
- 2015-2016: Vice President, Academia Sinica
- 2006-2011: Distinguished Research Fellow and Vice President (Academic), Academia Sinica
- 2005: Fellow, The Third World Academy of Sciences (TWAS)
- 2000-2015: Distinguished Research Fellow, Institute of Biological Chemistry, Academia Sinica
- 2000-2006: Director, Institute of Biological Chemistry, Academia Sinica
- 2000: Academician, Academia Sinica
- 1996-1997: Acting Head, Dept. of Cell & Structural Biology, UIUC
- 1988-2000: Professor of Biophysics, Biochemistry and Chemistry, Dept. of Cell & Structural Biology, Biochemistry, UIUC
- 1974-1988: Postdoctoral Research Associate (74-80), Research Scientist (80-82), Principal Research Scientist (82-85), Senior Research Scientist (85-88), Department of Biology, MIT

Representative Publications

1. Wang, H. C., Chou, C. C., Hsu, K. C., Lee, C. H., and Wang, A. H. (2019) New paradigm of functional regulation by DNA mimic proteins: Recent updates. *IUBMB Life* **71**, 539-548
2. Lee, C. C., Yang, C. Y., Lin, L. L., Ko, T. P., Chang, A. H., Chang, S. S., and Wang, A. H. (2019) An effective neutralizing antibody against influenza virus H1N1 from human B cells. *Scientific reports* **9**, 4546
3. Lee, C. C., Ko, T. P., Chen, C. T., Chan, Y. T., Lo, S. Y., Chang, J. Y., Chen, Y. W., Chung, T. F., Hsieh, H. J., Hsiao, C. D., and Wang, A. H. (2019) Crystal structure of PigA: A prolyl thioester-oxidizing enzyme in prodigiosin biosynthesis. *Chembiochem : a European journal of chemical biology* **20**, 193-202
4. Lee, C. H., Shih, Y. P., Ho, M. R., and Wang, A. H. (2018) The C-terminal D/E-rich domain of MBD3 is a putative Z-DNA mimic that competes for Zalpha DNA-binding activity. *Nucleic acids research* **46**, 11806-11821.
5. Chan, Y. T., Ko, T. P., Yao, S. H., Chen, Y. W., Lee, C. C., and Wang, A. H. (2017) Crystal structure and potential head-to-middle condensation function of a Z,Z-farnesyl diphosphate synthase. *ACS Omega* **2**, 930-936
6. Wang, H. C., Ho, C. H., Chou, C. C., Ko, T. P., Huang, M. F., Hsu, K. C., and Wang, A. H. J. (2016) Using structural-based protein engineering to modulate the differential inhibition effects of SAUGI on human and HSV uracil DNA glycosylase. *Nucleic acids research* **44**, 4440-4449
7. Lee, C. H., Chou, C. C., Hsu, M. F., and Wang, A. H. (2015) Determining the N-terminal orientations of recombinant transmembrane proteins in the *Escherichia coli* plasma membrane. *Scientific reports* **5**, 15086
8. Chou, C. C., and Wang, A. H. (2015) Structural D/E-rich repeats play multiple roles especially in gene regulation through DNA/RNA mimicry. *Molecular bioSystems* **11**, 2144-2151
9. Lee, C. C., Maestre-Reyna, M., Hsu, K. C., Wang, H. C., Liu, C. I., Jeng, W. Y., Lin, L. L., Wood, R., Chou, C. C., Yang, J. M., and Wang, A. H. (2014) Crowning proteins: modulating the protein surface properties using crown ethers. *Angewandte Chemie* **53**, 13054-13058
10. Chen, K. E., Lin, S. Y., Wu, M. J., Ho, M. R., Santhanam, A., Chou, C. C., Meng, T. C., and Wang, A. H. (2014) Reciprocal allosteric regulation of p38gamma and PTPN3 involves a PDZ domain-modulated complex formation. *Science signaling* **7**, ra98

