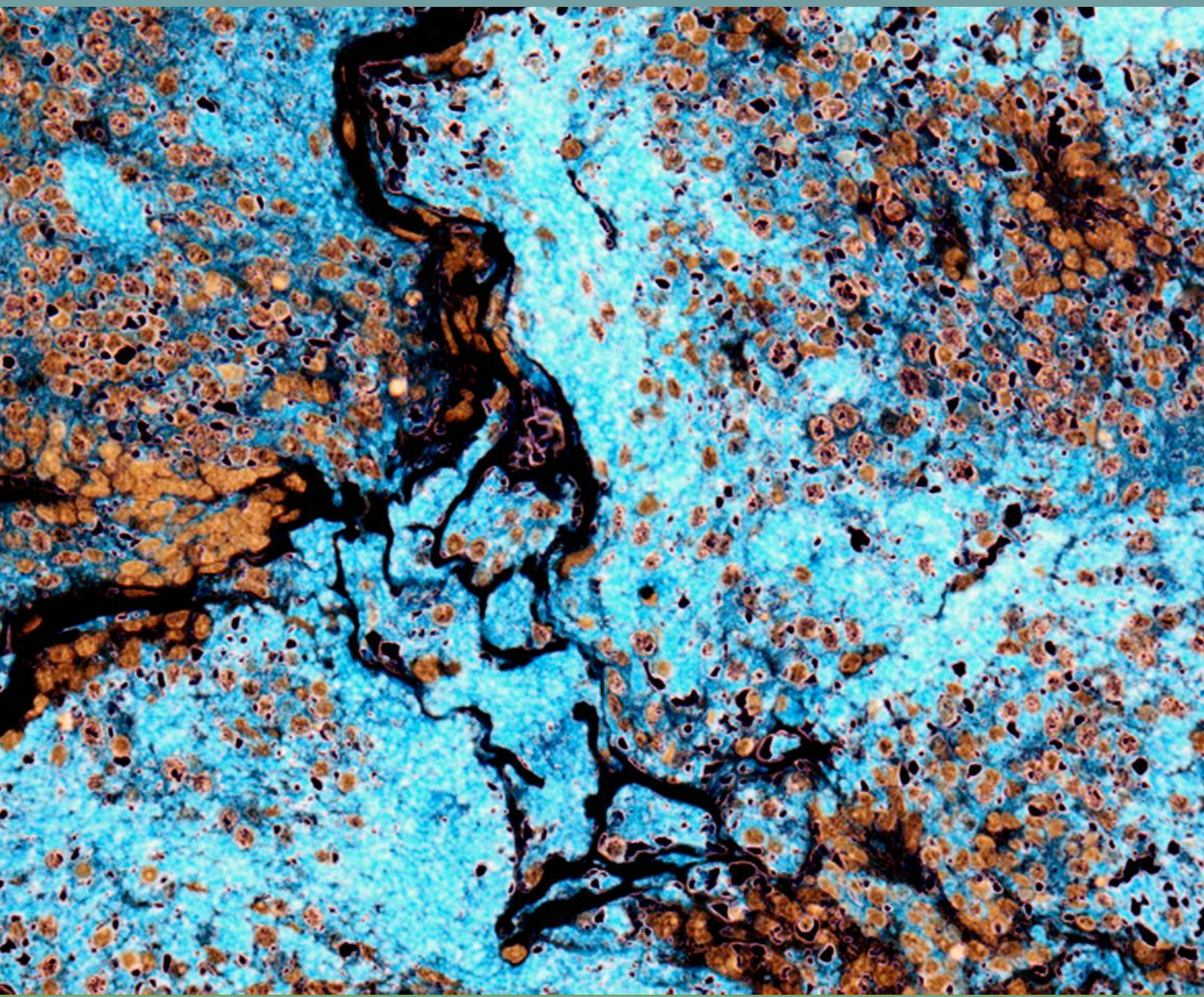
BIOMEDICAL MOLECULAR IMAGING & 11TH MOLECULAR IMAGING CENTER

BMI 2021



SUNDAY, DECEMBER 19, 2021

Cisco Webex 雲端視訊會議

國立臺灣大學分子生醫影像研究中心

BMI2021

雲端會議連結通知

- 會議時間：2021 年12 月19 日 (星期日) 上午9:20-下午4:30
- 會議連結：Cisco Webex雲端視訊會議 (請點選網址)

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BMI 2021 第 11 屆 分子生醫影像學術研討會

Biomedical Molecular Imaging & 11th Molecular Imaging Center Symposium

Program of BMI 2021 - Sun., December 19th , 2021

Time	Schedule		
09:20-09:30	***Registration***		
09:30-09:40	***Opening Remarks*** **CHEN, Hsien-Yeh 陳賢燁 教授/主任** *National Taiwan University*		
Time	**Title**	**Speakers**	**Session Chair**
09:40-10:05	**Plenary Lecture 1** **High speed volumetric imaging of brain**	**CHU, Shi-Wei** **朱士維 教授/副主任** *National Taiwan University*	**CHEN, Hsien-Yeh** **陳賢燁 教授/主任** *National Taiwan University*
10:05-10:20	**Invited Speaker 2** **Potential Applications of Biomedical Molecular Imaging in the Diagnostics of Sensorineural Hearing Loss**	**WU, Chen-Chi** **吳振吉 醫師** *National Taiwan University Hospital*	
10:20-10:35	**Invited Speaker 3** **Advancements in CZT Myocardial Perfusion Imaging**	**KO, Chi-Lun** **柯紀綸 醫師** *National Taiwan University Hospital*	
10:35-10:50	**Invited Speaker 4** **Targeting Extracellular Stiffness and Myofibroblast Contractility to Attenuate Airway Fibrosis**	**LIN, Yu-Chun** **林育君 教授** *National Taiwan University*	
10:50-11:00	***Break***		
11:00-11:15	**Invited Speaker 5** **Harnessing nanotopographies to influence stem cell differentiation**	**WANG, Peng-Yuan** **王鵬元 教授** *Oujing Laboratory*	**CHU, Shi-Wei** **朱士維 教授/副主任** *National Taiwan University*
11:15-11:30	**Invited Speaker 6** **PET as Imaging Biomarker in Pancreatic and Periampullary Neoplasms**	**CHENG, Mei-Fang** **鄭媚方 醫師** *National Taiwan University Hospital*	
11:30-11:45	**Invited Speaker 7** **Medical Device Innovation from Concept to Market: Esophageal Applicator**	**CHANG, Vic** **張維哲 CEO** *BRAXX Biotech Co., Ltd.*	
11:45-12:00	**Invited Speaker 8** **Advancements in the Development and Application of Semiconductor Hybrids**	**K.P.O. Mahesh** **馬哈旭 博士** *National Taiwan University*	

12:00-13:45	***Lunch***		
13:45-14:10	**Plenary Lecture 9** **Seeing is counting? Solving the chain number puzzle of wood cellulose microfibrils**	**TAI, Hwan-Ching** **戴桓青 教授** *National Taiwan University*	**CHIANG, Yu-Chih** **姜昱至 醫師/副主任** *National Taiwan University Hospital*
14:10-14:25	**Invited Speaker 10** **Diagnostic Amyloid PET/MRI Acquired with ~2% Standard Dose using Deep Learning**	**CHEN, Kevin T.** **程子翔 教授** *National Taiwan University*	
14:25-14:40	**Invited Speaker 11** **Development of bioactive parylene porous scaffold for vital pulp therapy**	**YEH, Hsiao-Wen** **葉筱雯 醫師** *National Taiwan University Hospital*	
14:40-14:55	**Invited Speaker 12** **The Investigation of Imaging Spectrum and Implicated Pathophysiology in Cerebral Amyloid Angiopathy**	**Hsin-Hsi Tsai** **蔡欣熹 醫師** *National Taiwan University Hospital*	
14:55-15:05	***Break***		
15:05-15:20	**Invited Speaker 13** **WNT2B promotes fetal placental vascularization by inducing intravillous angiogenesis in ruptured tubal ectopic pregnancy**	**Lin, Chao-Po** **林照博 教授** *ShanghaiTech University*	**LIU, Tzu-Ming** **劉子銘 教授** *University of Macau*
15:20-15:35	**Invited Speaker 14** **Chronic intravital two-photon imaging for studying the dynamics of the central nervous system in behaving mice**	**WU, Yu-Wei** **吳玉威 博士** *Academia Sinica*	
15:35-15:50	**Invited Speaker 15** **Label-free Visualization of Cell Senescence**	**LIU, Tzu-Ming** **劉子銘 教授** *University of Macau*	
15:50-16:05	**Invited Speaker 16** **Development of New Waveform Spinal Cord Stimulator for Prolonged Pain-relief**	**CHANG, Tina** **張雅婷 Director** *APrevent Medical*	
16:05-16:20	**Invited Speaker 17** **小動物正子/電腦斷層掃描造影在胰臟肝轉移診斷的臨床前研究**	**HO, Being** **何秉穎 技術長** *Primo Biotechnology Co., Ltd*	
16:20-16:30	***Closing Remarks*** **CHEN, Hsien-Yeh 陳賢燁 教授/主任** *National Taiwan University*		

Plenary Speaker 1

High speed volumetric imaging of brain

Shi-Wei Chu

[1]*Department of Physics, National Taiwan University.*
[2]*Molecular Imaging Center, National Taiwan University.*
[3]*Brain Research Center, National Tsing Hua University.*

Understanding how the brain functions is one of the grand challenges in modern scientific research. Similar to a computer, a functional brain is composed of hardware and software. The major bottleneck lies in the difficulty to directly observe the brain "software", i.e. the rule and operating information used by the brain, that might emerge from pan-neuron/synapse connectome. A recognized strategy for probing functional connectome is to perform volumetric imaging in brains with high spatiotemporal resolution and deep brain penetration. The underlying bottleneck, in my perspective, is that brain is composed of thousands to millions of densely interconnected neurons, spanning millimeter to centimeter with continuous spiking activities, and no suitable tool is able to study neural connections and activities *in vivo with* 3D subcellular resolution in any location of a living brain. The challenges include not only penetration depth but also imaging speed of neural networks [1].

For thick-tissue cellular observation in neuroscience, two-photon microscopy (2PM) has become a mainstream imaging technique. Here we report our recent progresses in enhancing volumetric imaging speed of 2PM [2], with a model animal *Drosophila*, which offers a small brain with sophisticated function and genetic control capabilities. By incorporating optogenetic stimulation tools and an independent optical stimulation path, we demonstrated all-optical physiology in the visual pathway of *Drosophila* [3]. Furthermore, to allow volume imaging deep inside a mammal brain, which is typically centimeter in scale, we develop two-photon volumetric endoscopy [4] by integrating two gradient index lenses, allowing in vivo imaging of neural circuits in centimeter-depth brain regions with high-contrast and sub-second volume rate. If time allows, I would like to introduce our very recent results on upgrading the volumetric speed to be larger than 500-volumes/second over $10^7 \mu m^3$ size, via combination of 32-beam parallel lateral-scanning, a ~100-kHz axial-scanning acoustic lens, and a 32-channel photodetector, enabling data rate above 10 GHz.

References

1. S.-H. Huang, N. Irawati, Y.-F. Chien, J.-Y. Lin, Y.-H. Tsai, P.-Y. Wang, L.-A. Chu, M.-L. Li, A.-S. Chiang, K. Tsia, and S.-W. Chu*, "Optical Volumetric Brain Imaging: Speed, Depth, and Resolution Enhancement" J. Phys. D 54, 323002 (2021). **Invited Topical Review**
2. K.-J. Hsu, Y.-Y. Lin, Y.-Y. Lin, K. Su, K.-L. Feng, S.-C. Wu, Y.-C. Lin, A.-S. Chiang, S.-W. Chu*, "Millisecond two-photon optical ribbon imaging for small-animal functional connectome study" Opt. Lett. 44, 3190-3193 (2019). **Editor's pick**
3. C. Huang, C.-Y. Tai, K.-P. Yang, W.-K. Chang, K.-J. Hsu, C.-C. Hsiao, S.-C. Wu, Y.-Y. Lin*, A.-S. Chiang*, and S.-W. Chu*, "All-optical volumetric physiology for connectomics in dense neuronal structures" iScience 22, 133-146 (2019)
4. Y.-F. Chien, J.-Y. Lin, P.-T. Yeh, K.-J. Hsu, Y.-H. Tsai, S.-K. Chen*, and S.-W. Chu*, "Dual GRIN lens two-photon endoscopy for high-speed volumetric and deep brain imaging" Biomed. Opt. Exp., 12, 162-172 (2021).

Invited Speaker 2

Potential Applications of Biomedical Molecular Imaging in the Diagnostics of Sensorineural Hearing Loss

Chen-Chi Wu[1)]

1)Department of Otolaryngology, National Taiwan University Hospital, Chung-Shan South Rd, Taipei 100, Taiwan

Hearing loss is the most common sensory deficit in humans, representing the third most common health defects in adults, after cardiovascular diseases and arthritis. The WHO reported that approximately 466 million people (432 million adults and 34 million children) worldwide have disabling hearing loss, and the data will increase to an estimated 900 million by 2050. Hearing loss can be classified into three types: conductive hearing loss, sensorineural hearing loss (SNHL), and mixed hearing loss. Among them, SNHL is the most common, accounting for approximately 90% of the total hearing loss cases. However, current diagnostics and therapeutics for SNHL have been impeded by the human cochlea's inaccessibility for in vivo imaging, resulting from its extremely small size, convoluted coiled configuration, and deep encasement in dense bone.

Over the past two decades, my team and I have been dedicated to better detection, diagnosis, and management of SNHL. Our work includes clinical genetic studies, translational studies, and basic animal studies, covering a wide but continuous range of research interests in this field. To explore the pathophysiology and potential therapeutic strategies, we have generated several strains of cell-lines and mouse models with various genetic or acquired SNHL. By applying recent advances in biomedical molecular imaging, such as fMRI, micro-optical coherence tomography (μOCT), and two-photon fluorescence microscopy (TPFM), to these experimental models, it can be anticipated that the pathogenetics and therapeutics of SNHL will be further elucidated. In this talk, I will present our previous effort on these experimental platforms, and then discuss potential applications of biomedical molecular imaging in the diagnostics of SNHL.

Invited Speaker 3

Advancements in CZT Myocardial Perfusion Imaging

Chi-Lun Ko

Department of Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan

Myocardial perfusion imaging (MPI) is widely used in the diagnosis of coronary artery disease (CAD) and in accessing the risk of cardiovascular disease. The introduction of cardiac cadmium-zinc-telluride (CZT) cameras has greatly reduced the acquisition time of MPI while preserving the diagnostic accuracy. However, many innate problems of MPI, such as motion artifacts, relative measurements, high radiation dosimetry, and suboptimal correlation with anatomical images, remained unsolved.

To overcome motion artifacts, we developed a data-driven motion correction technique to compensate both respiratory motion and cardiac motion. The resulting dual motion frozen images outperformed uncorrected images in the diagnosis of CAD. On the other hand, patients with multivessel disease may exhibit balanced ischemia and cause falsely negative results of MPI. We took advantage of this CZT camera and developed a dynamic imaging protocol to quantify absolute myocardial blood flow and flow reserve from Tl-201 MPI. This technique can also improve the diagnostic performance of MPI.

As the growth of computing power, artificial intelligence with deep neural networks has became more implementable. We applied this technique to develop models to reduce noise from ultra-low dose MPI. This allowed as many as 90% dose reduction while the diagnostic performance was preserved. To correlate functional MPI and anatomical images, such as coronary CT angiography (CCTA), we built up a large and co-registered multimodality image database. With this database, we trained deep learning models to align these vastly different types of images. And we also use deep learning model to trace vessels to facilitate image interpretation.

Invited Speaker 4

Targeting Extracellular Stiffness and Myofibroblast Contractility to Attenuate Airway Fibrosis

Yuchun Lin

Institute of Medical Device and Imaging, National Taiwan University, Taipei, Taiwan

Microenvironment of all adherent cells alters cell's phenotype, proliferation, gene expression, and cell fate. Increase deposition of ECM protein by fibroblast or myofibroblasts increases stiffness of cellular microenvironment, which might be not only be the results of but also the cause of tissue fibrosis. Subsequent matrix synthesis may generate positive feedback that leads to persistent fibroblast activation and thus fibrosis. Accumulation of ECM proteins in chronic rejected allograft in lung transplant may increase the stiffness of tissue and result in further unbalance of proteins turnover and fibrous obliteration of the airway. We hypothesized that simultaneously targeting myofibroblast contractility with relaxin and ECM stiffness with lysyl oxidase inhibitors could break the feedback loop, reversing established fibrosis. To test this, we used the orthotopic tracheal transplantation (OTT) mouse model, which develops robust fibrotic airway remodeling. Mice with established fibrosis were treated with saline, mono-, or combination therapies. Although monotherapies had no effect, combining these agents decreased collagen deposition and promoted re-epithelialization of remodeled airways. Relaxin inhibited myofibroblast differentiation and contraction in a matrix-stiffness–dependent manner through prostaglandin E2 (PGE2). Furthermore, the effect of combination therapy was lost in PGE2 receptor knockout and PGE2-inhibited OTT mice. This study revealed the important synergistic roles of cellular contractility and tissue stiffness in the maintenance of fibrotic tissue and suggests a new therapeutic principle for fibrosis.

Invited Speaker 5

Harnessing nanotopographies to influence stem cell differentiation

Peng-Yuan Wang

Oujing Laboratory, Wenzhou, China
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Manipulation of cell fate is a critical process in regenerative medicine and cell therapies. Strategies in maintaining the stemness of stem cells and directing stem cells into specific cell types are limited. To date, a number of studies have reported that biophysical cues in the form of surface nanotopographies can influence stem cell attachment, proliferation, and differentiation. Specific surface nanotopographies can enhance the efficiency of cell reprogramming or maintain stemness of stem cells. While biochemical cues are generally efficient, biophysical cues have advantages such as scalability, cost-effectiveness, and longer lifetime, while they are also easy to be defined. In our group, we fabricated biomimetic structures, including nanogrooves, nanopillars, nanopores, and colloidal crystals using various nanotechnologies. Our results show that controlling surface nanotopographies and chemistry can direct cell fate decisions, which reveals the fundamental questions in cell biology and benefits cell therapy. We believe that combining optimal biophysical cues with current biological approaches has great potential to generate functional cells and benefit regenerative medicine and cell therapies.

Invited Speaker 6

PET as Imaging Biomarker in Pancreatic and Periampullary Neoplasms

Mei-Fang Cheng[1], Ruoh-Fang Yen[1], Chyng-Yann Shiue[1], Yu-Wen Tien[2]

Department of Nuclear Medicine[1] and Surgery[2], National Taiwan University Hospital and College of Medicine

Pancreatic neoplasms can arise from both exocrine and endocrine cells. Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic exocrine neoplasm. Surgical resection remains the mainstay treatment for curative intention in patients without distant organ metastases. However, approximately 10-20% of PDAC patients are discovered to have unanticipated metastases at the time of laparoscopy or laparotomy. Furthermore, over 76% of patients who undergo surgical resection will develop metastatic disease as the first evidence of disease recurrence and more than half of the metastases occur within 6 months after operation. The fact that liver metastases develop so soon after surgery suggests that cancer cells have already metastasized, and currently-available imaging tools can't detect these micro-metastases. Operation on patients with micro-metastatic disease will subject them to operative risk without any benefit in survival. One method of screening out liver micro-metastatic disease can avoid these unnecessary operations. The glucose analogue, 2-deoxy-[18F]fluorodeoxyglucose (FDG), is routinely used in positron emission tomography (PET). However, many tumors show low glycolytic activities, uptake not exceeding physiologic background or high activity in inflammatory tissues mimicking malignancy. To overcome these limitations, suitable PET tracers other than FDG targeting tumor metabolism beyond enhanced glycolysis need to be exploited. (4S)-4-(3-[18F]fluoropropyl-)-L-glutamate (FSPG) is a ^{18}F-labeled glutamate derivative targeting system Xc- transporter (xCT). Our preliminary clinical trial in patients with PDACs revealed FSPG PET is superior to FDG PET in detecting metastasized PDAC, especially in the liver.

Although uncommon, neuroendocrine neoplasms (NENs) that arose from pancreatic endocrine cells can cause significant morbidity due to hormone secretion. These tumors can be very small and difficult to detect by conventional anatomical imaging. On the other hands, non-functional NENs usually do not incur symptoms/signs until they grow large in enough, 30-50% of these tumors are at an advanced stage at the time of diagnosis. More than 90% of NENs express somatostatin receptors (SSTRs), especially type 2. PET imaging using ^{68}Ga-DOTATOC (DOTATOC) is a radiotracer that targets SSTR2 and SSTR5. DOTATOC PET offers high sensitivity and specificity in detecting NENs expressing SSTR2 and 5. For tumors that cannot be completely resected or showed distant metastases, patients can be further treated with somatostatin analogues, chemotherapy, target therapies or peptide receptor targeted radiotherapy (PRRT). DOTATOC PET provides whole-body assessment of the abundance of SSTR2 in the tumors, hence directs therapy management and impacts on patient survival. In contrast, 18F-flurodeoxyglucose (FDG) detects tumors that exhibit high proliferation rate and NENs that do not express SSTRs. Chemotherapy is the treatment of choice for these aggressive NENs.

Invited Speaker 7

Medical Device Innovation from Concept to Market: Esophageal Applicator

Vic Chang

BRAXX Biotech Co., Ltd., Taiwan

Innovative medical device development is always a challenge, which would take several years to reach the stage of commercialization. BRAXX Biotech develops an Esophageal Applicator which is mainly used for the brachytherapy of esophageal cancer. It can be simply performed in hospital clinic and improve precise positioning of radioactive sources, elevating efficiency and reducing side effects. Here I will share the experience of how BRAXX reach the point of market access.

Invited Speaker 8

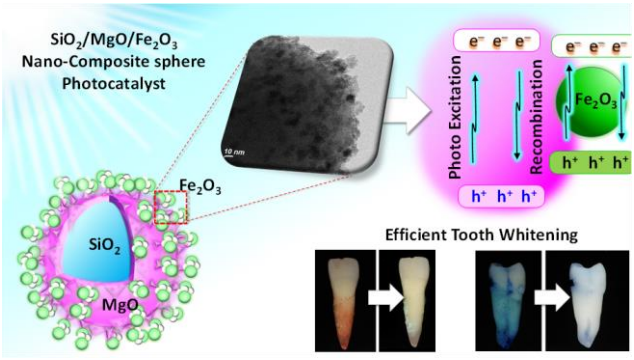
Advancements in the Development and Application of Semiconductor Hybrids

K.P.O. Mahesh,[1] and Yu-Chih Chiang[2]

[1]Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan, [2]Molecular Imaging Center, National Taiwan University, Taipei 10617, Taiwan

Semiconductors have brought a revolution in the fields such as electronics, biosensors and photocatalysts. Perovskite based semiconductor materials research currently mostly focuses in the fields of solar cells, optical sensors, light-emitting diodes and lasers. Metal oxide, metal sulfide and metal doped semiconductors are being extensively researched for their potential applications in energy storage device, gas storage, photocatalysis as well as in electrocatalysis. In this presentation, we only pick selected examples from our published research articles to demonstrate the synthesis, applications and durability of as-fabricated devices.

The perovskite materials are sensitive to polar solvents, moisture, and heat. As a result, they are not suitable for extrusion 3D printing. In this report, perovskite nanocrystals of $HC(NH_2)_2PbBr_3$ ($FAPbBr_3$) and $FAPb\text{-}(Br_{0.36}I_{0.63})_3$ were encapsulated using a variety of thermoplastics for 3D printing filaments that were investigated to test their capability as protective encapsulation materials for perovskite nanocrystals. It is observed that polycaprolactone exhibited excellent protective properties, and the perovskite nanocrystal−PCL composites could be processed into fluorescent objects and micrometer-sized fluorescent fibers via extrusion 3D printing.[1] For the fabrication of flexible biosensor, we fabricate a hybrid structure, by directly growing the $\alpha\text{-}Fe_2O_3$ nanoparticles on the surface of flexible carbon cloth as an electrode for the detection of dopamine. The results showed that the ACC-α-Fe2O3 electrode exhibits impressive electrochemical sensitivity, stability and selectivity for the detection of dopamine.[2] For the photocatalytic degradation of industrial dyes, we have synthesized metal doped metal oxide nanospheres and showed effective photocatalytic activity in degradation of Acid Black 1 dye and discoloration human tooth under UVA-light irradiation.[3]



Reference

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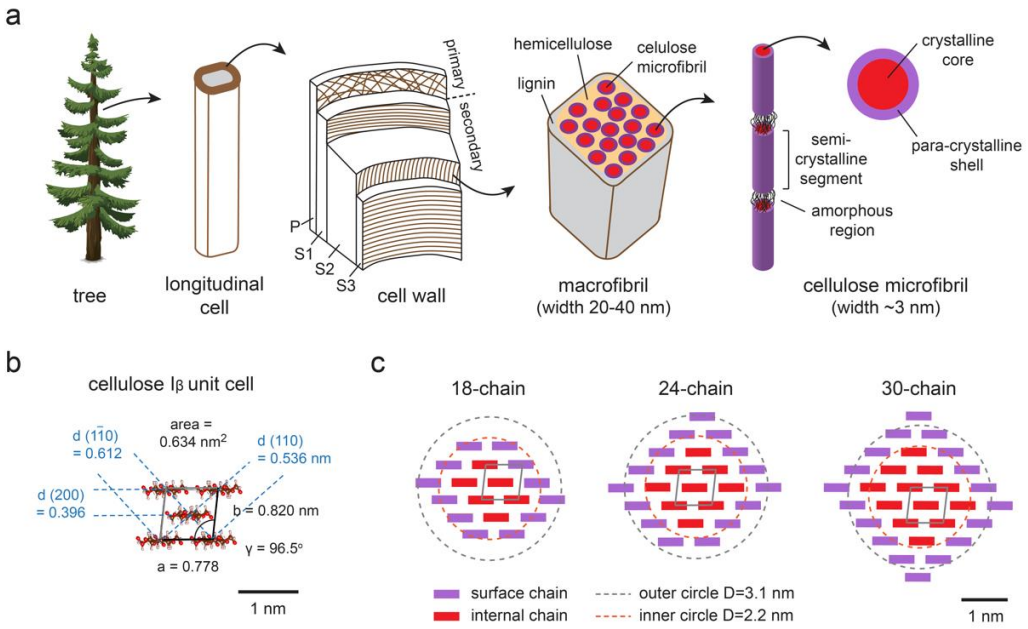
Pleanary Speaker 9

Seeing is counting? Solving the chain number puzzle of wood cellulose microfibrils

Chih-Hui Chang [1], Cheng-Si Tsao [2], Hwan-Ching Tai[1]

[1)]Department of Chemistry and [2)]Department of Mechanical Engineering, National Taiwan University, Taipei, Taiwan

Wood cellulose, the most abundant organic substance on earth, is synthesized by enzymes with six-fold symmetry, so the expected chain number (N) per cellulose microfibril (CMF) is multiples of six. Although many methods have been applied to measure CMF sizes in wood, the N value remains controversial, resulting in confusions about CMF nanostructures. Here, we developed new methods to measure the cross-section area and aspect ratio of crystalline core zones in CMFs of intact wood using small-angle X-ray scattering (SAXS). The 1:1 aspect ratio showed that CMFs remained segregated. We also devised a new method to assess N by combining core area estimates and degrees of crystallinity estimated by solid-state nuclear magnetic resonance. Our results suggest N = 24 for the majority of wood CMFs, which is conserved between gymnosperm and angiosperm trees. In contrast, current consensus models of wood CMFs proposed these features: N = 18, fibril fusion to increase apparent thickness, and apparently thicker fibrils in angiosperms over gymnosperms; but our results proved them incorrect. In naturally and artificially aged woods, using the combination of SAXS and X-ray diffraction, we only observed CMF aggregation (contact without crystalline continuity) but not fusion (forming conjoined crystalline unit). This further argued against the existence of partially fused CMFs in the first place. The average CMF found in new wood has a crystalline core with ~2.2 nm diameter and a para-crystalline shell of ~0.45 nm thickness. Our findings are important for advancing wood structural knowledge and more efficient utilization of wood resources in sustainable bio-economies.



Invited Speaker 10

Diagnostic Amyloid PET/MRI Acquired with ~2% Standard Dose using Deep Learning

Kevin T. Chen[1,2], Tyler N. Toueg[2], Mary Ellen I. Koran[2], Guido Davidzon[2], Michael Zeineh[2], Dawn Holley[2], Harsh Gandhi[2], Kim Halbert[2], Athanasia Boumis[2], Gabriel Kennedy[3], Elizabeth Mormino[3], Mehdi Khalighi[2], Greg Zaharchuk[2]

[1] *Biomedical Engineering, National Taiwan University, Taipei, Taiwan*

[2] *Radiology, Stanford University, Stanford, CA, United States*

[3] *Neurology and Neurological Sciences, Stanford University, Stanford, CA, United States*

Purpose

We have previously trained an ultra-low-dose amyloid PET/MRI U-Net based on simulated low-dose data [1]. Here, we demonstrate that the network performs similarly using actual ultra-low injected dose [2].

Materials and Methods

Data Acquisition: 40 datasets (39 participants, 19 female; 67±8 years) were recruited for simultaneous amyloid (^{18}F-florbetaben) PET/MRI (T1-, T2-, T2 FLAIR-weighted) scanning on a time-of-flight PET/MRI scanner (Signa PET/MRI, GE Healthcare). List-mode PET data (90-110 minutes post-injection) were reconstructed for the full-dose image and also randomly undersampled by a factor of 100 to reconstruct low-dose (1% dose) PET images. 18 participants (9 female, 72±9 years) were also recruited for two PET/MRI acquisitions, one low-dose acquisition (6.6±3.6 MBq, 2.2%±1.3% dose) followed by a full-dose (300±14 MBq) one.

U-net Implementation: A low-dose PET/MRI U-net [3] was pre-trained with simulated data [1] and further fine-tuned with low-dose acquisition data (100 epochs, learning rate=0.0001). Leave-one-out was used during network fine-tuning.

Data Analysis: Four board-certified clinicians rated amyloid uptake status (+/-) as well as image quality on a 5-point scale for ultralow dose, deep learning enhanced ultra-low-dose, and full dose scans. The image quality metrics peak signal-to-noise ratio (PSNR), structural similarity (SSIM), and root mean square error (RMSE) were calculated using full-dose as ground-truth.

Results

All deep learning enhanced images had reduced noise and improved image quality score compared with their ultra-low-dose counterparts. Diagnostic accuracy using the enhanced images was high (97.2%). Quantitatively, image quality as indicated by all three metrics improved dramatically for all datasets.

Conclusion

With the help of trained deep learning networks, we were able to produce diagnostic amyloid PET images acquired with markedly reduced injected radiotracer dose.

References

[1] Chen KT, et al. *Radiology* 2019. [2] Chen KT, et al. *Eur J Nucl Med Mol Imaging* 2021. [3] Ronneberger O, et al. arXiv 2015.

Invited Speaker 11

Development of bioactive parylene porous scaffold for vital pulp therapy

Hsiao-wen Yeh,[1)] Hsien-Yeh Chen,[2)] and Yu-Chih Chiang[1)]

[1)]Department of Dentistry, National Taiwan University, No.1, Changde St., Taipei, Taiwan R.O.C
[2)]Chemical Engineering, National Taiwan University, No.1, Sec.4, Roosevelt Rd. Taipei, Taiwan R.O.C

Introduction: Maintaining pulp vitality during restorative and endodontic procedures is a recently emerged concept that has been termed vital pulp therapy (VPT). This involves covering the pulpal surface with a dental material to facilitate the formation of reparative dentin (1). The purpose of this research was to develop novel biomaterials, specifically a designable, growth factor (GFs) and dental pulp stem cell (DPSC) carriable 3-D porous parylene scaffold (PPxS), for use in vital pulp therapy.

Results: The results revealed that the pore size and porosity of PPxS and PPxS-GFs were similar and both showed good cell viability and biocompatibility. However, the PPxS-treated pulp showed significantly higher cell proliferation. Micro-CT analysis of the study animals showed mineralized tissue formed beneath the cavity in the pulp tissue in the PPxS/DPSC, PPxS-GFs, and PPxS-GFs/DPSC groups.

Discussion: In this study we loaded two growth factors on a parylene scaffold along with DPSCs and expected a better effect on dentin-pulp complex regeneration. The dosages of growth factors Wnt3a and FGF-2 used in the *in vitro* assay had the potential to induce odontoblast differentiation and, based on the micro-CT images, promoted mineralized tissue *in vivo*. These effects may have been caused by the combination of the good biocompatibility and porous structure of the parylene, the effects of the growth factors, and the regenerative potential of the DPSCs.

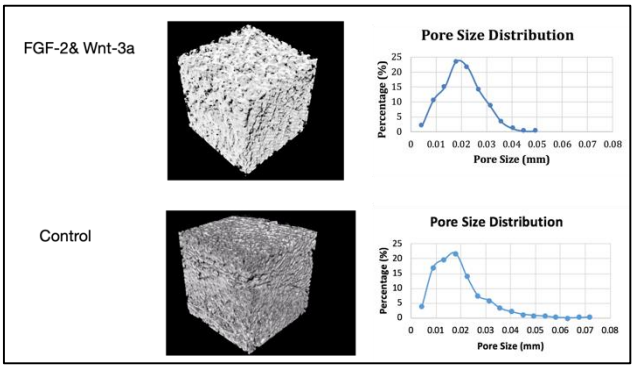


Fig.1 3-D Micro-Structure Analysis.

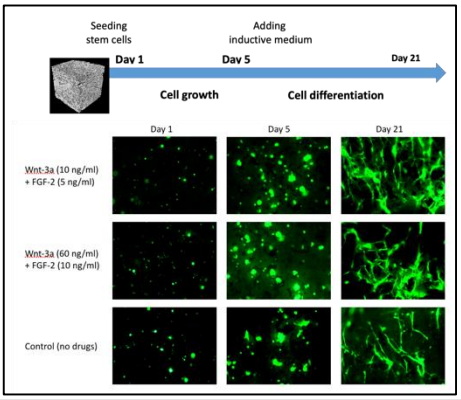


Fig.2 DPSCs cultured on PPxS with both Wnt3a (10ng/ml) and FGF-2 (5ng/ml), Wnt3a (60ng/ml) and FGF-2 (10ng/ml), and without treatment (control group).

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Invited Speaker 12

The Investigation of Imaging Spectrum and Implicated Pathophysiology in Cerebral Amyloid Angiopathy

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Cerebral amyloid angiopathy (CAA), the major etiology of spontaneous lobar intracerebral hemorrhage (ICH), is caused by deposition of β-amyloid (Aβ) in the leptomeningeal and cortical small vessels of the brain. To understand its imaging spectrum and potential pathophysiology, we investigate radiological features in CAA using a combined approach of multimodal neuroimaging techniques. We first identified CAA in patients presenting with mixed lobar and deep hemorrhages, and confirmed these patients harbor detrimental vascular outcome in the long-term, reinforcing its clinical significance in ICH population. We then expanded the current knowledge of CAA spectrum, showing that CAA can involve not only supratentorial, but also infratentorial small vessels in superficial cerebellar area. By showing the association between CAA and lacunar infarct, we further extended the parenchymal injury of CAA from hemorrhage to cerebral ischemia. All these findings may revolutionize current diagnostic standards for CAA.

To further understand the underlying pathogenic mechanisms, we investigated the perivascular space from both the perspective of transgenic mouse model and the clinical patient cohort. We compromised the lymphatic drainage route in the animal model, and demonstrated subsequently dilated perivascular space and exacerbated vascular amyloid deposition. This finding is compatible with our observations in the clinical CAA patients, showing MRI-visible enlarged perivascular spaces were positively correlated with the load of cerebrovascular Aβ. We confirmed that perivascular lymphatic drainage to the cervical lymph nodes functions as a pathway for vascular Aβ clearance and may have translational potential for developing future therapeutic strategy.

Since inflammatory cells, especially for myeloid-lineage ones, may participate in the function of lymphatic drainage system, we then investigated the contribution of microglia/macrophage on CAA and cerebral small vessel disease. We measured the plasma soluble form triggering receptor expressed on myeloid cells 2 (sTREM2), which is considered as an essential signalling pathway to compact and clear parenchymal Aβ. We confirmed that peripheral TREM2 response is associated with small vessel disease-related white matter lesions independent of cerebral amyloid and tau. Interestingly, cognitive protective effect of TREM2 signalling is observed in Aβ disorders with present tau-mediated neurodegeneration, suggesting that innate immune response may be another therapeutic target in treating CAA and its long-term neurodegenerative outcome.

Invited Speaker 13

WNT2B promotes fetal placental vascularization by inducing intravillous angiogenesis in ruptured tubal ectopic pregnancy

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Abstract

Throughout intrauterine pregnancy (IP), intervillous and intravillous vascular networks at the maternal-fetal interface ensure sufficient exchange of gas and nutrients, supporting the optimal growth of the fetus. Here, we show that in tubal ectopic pregnancy (TEP), a severe pregnancy complication accounting for 9-13% pregnancy-related deaths due to implantation and embryonic growth in fallopian tubes, is strongly associated with altered villous vascularization. The severity of TEP is correlated with the extent of villous vascularization. Specifically, we observed extensive vascular development in villi of patients with ruptured tubal ectopic pregnancy (REP), characterized by continuous fetal growth, deep invasion of trophoblasts, and rupture of the fallopian tubes. By contrast, in non-ruptured ectopic pregnancy (nREP), a treatable, less severe TEP, villous blood vessels remain minimal. By performing multiple vasculogenesis and angiogenesis assays using clinical tissue explants and organoid cultures, we identified a novel pro-angiogenic factor secreted by trophoblasts, WNT2B, that promotes villous vasculogenesis and angiogenesis by inducing endothelial cell differentiation and VEGF expression in endothelial cells. Furthermore, inhibition of Wnt signaling or progesterone pathway blocks generic angiogenesis/vasculogenesis. These findings reveal a major role for WNT-mediated angiogenesis in pregnancies, suggesting its value as a diagnostic marker for REP and as a potential therapeutic target.

Invited Speaker 14

Chronic intravital two-photon imaging for studying the dynamics of the central nervous system in behaving mice

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To understand how the brain works, it is crucial to monitor the brain's activity in behaving animals. Our lab focuses on understanding the principle of neural network re-organized underlying motor control and learning. This re-organization includes changes in neuronal synaptic connections and biochemical and electrophysiological activities of neurons and glial cells. We combined *in vivo* two-photon imaging with different behavioral tasks to monitor the synaptic structural plasticity and Ca^{2+} activity of the neurons and glial cells associated with learning through a chronic cranial window. A similar approach is used to monitor neural activity in the spinal cord and the dorsal root ganglia upon different sensory stimuli. We also combined gradient-index (GRIN) lens with two-photon imaging to study the role of the striatal neurons in the deeper brain regions, *i.e.* basal ganglia, which is essential for motor control. In addition, we study the role of Ca^{2+} signaling in a type of glial cells, astrocytes. We employed volumetric imaging of individual astrocytes and revealed a very complex repertoire of intracellular Ca^{2+} transients. The distributions of the spreading volume and duration of the Ca^{2+} transients follow a power law, a signature of self-organized criticality. In summary, our chronic intravital two-photon imaging approaches provide a window for linking the subcellular and cellular activity with animal behaviors as a crucial step toward understanding how our brain works.

Lab website: https://www.yuweiwu.org

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Invited Speaker 15

Label-free Visualization of Cell Senescence

Yinghan Yan [1)], Fuqiang Xing[1)], Ling Li[1)], Zhengying Gao [2)], Kai Miao [2,3,4)], Fangyuan Shao [1)], Chu-Xia Deng [2,3,4)*], Leo Tsz on Lee [2,4) *], Tzu-Ming Liu[1)*]

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Current drug sensitivity evaluation requires fixation and staining of cells to determine the dosages of significant apoptosis or necrosis. This snapshot observation freezes the cell metabolism and loses the time-course information of pharmacodynamics, which may discard the early signatures of apoptosis/necrosis. Here we develop a label-free method to report cell senescence by the endogenous lipofuscin-like autofluorescence. After treating cisplatin on MDA-MB-231 breast tumor cells, we found the two-photon lipofuscin-like red autofluorescence intensities (ex. @1100 nm; em. @600 nm) and corresponding lifetimes greatly increased with dosages and incubation time. Under the IC-50 dosage of 30 μM, the characteristic lipofuscin-like fluorescence appeared 24 hours earlier than the Annexin V/PI assay. The cell fate is already determined at the time when the lipofuscin-like fluorescence significantly increased. This signature also occurs for the drug-induced necrosis.

Then we applied our label-free approach to map the cell death in tumor spheroids, 3D tumor organoids, and 3D tumor slice culture that preserves the immune microenvironments. The pharmacodynamics of chemotherapy and anti-PD1/ anti-PDL1 immune checkpoint blockade therapy can be time-course monitored and successfully evaluated in the microenvironment. The translational potential on patient derived organoids was also investigated. Our results validate that the stress-induced acute accumulation of lipofuscin-like red autofluorescence could enhance the throughput of drug sensitivity test and expand the information dimension in the drug selection of cancer precision medicine. Details about how to differentiate apoptosis from necrosis and the occurrence timepoint of red autofluorescence with respect to caspase 3 signaling will be discussed in the presentation.

Invited Speaker 16

Development of New Waveform Spinal Cord Stimulator for Prolonged Pain-relief

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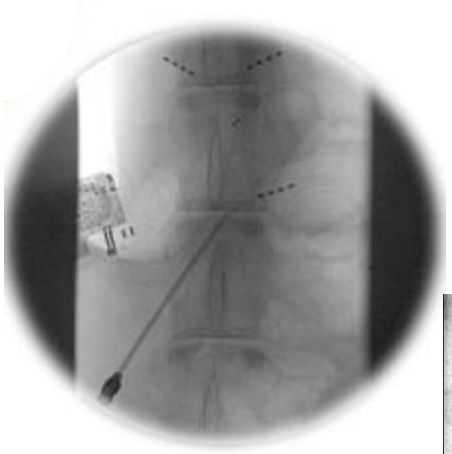
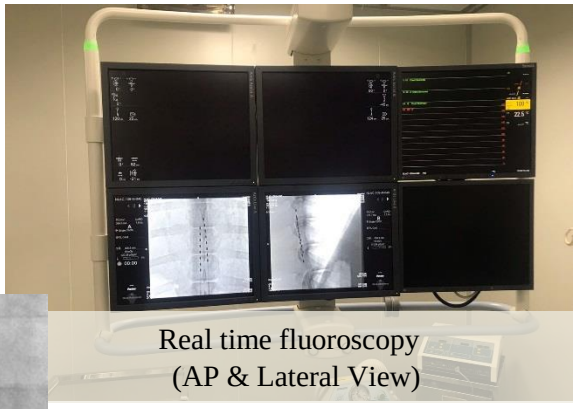
GIMER Medical, New Taipei City 221

Spinal Cord Stimulator (SCS) uses electrical pulses to interfere with pain perception transmission to and from the brain, thus reaching pain-relief effect; it has been in market since mid 1960's (by Medtronic). Traditional electrical stimulation frequency of SCS ranges from 50~1200 Hz. With the advancement of electronics industry, major improvement such as reduced implant size and strengthened power management came along. However, there was not much breakthrough in terms of waveform, expect for Nevro's 10kHz therapy (2014). GIMER Medical develops 500kHZ pulsed therapy to be delivered via SCS. This frequency was previously used in Pulsed Radiofrequency (PRF) devices, which are equipment in hospital or clinics but not implantable.

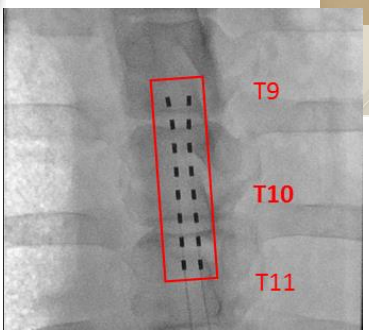
The development of a new therapy device is lengthy and usually needs several 'correction' after certain clinical feedbacks. GIMER's 500kHz SCS originally targets implantation at dorsal root ganglia (DRG), as other PRF devices. However, the implantation of DRG relies on surgeon skill and migration of the leads is often seen. Thus, we conducted feasibility test on animal (swine) and first in human to prove epidural lead implantation is effective in delivering GIMER waveform. The therapy was then changed to epidural implantation, which largely reduces the entry barrier for surgeons.



Leads of DRG implantation



Real time fluoroscopy
(AP & Lateral View)



Leads of epidural implantation

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Invited Speaker 17

小動物正子/電腦斷層掃描造影在胰臟肝轉移診斷的臨床前研究

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現今基礎醫學與臨床前研究仰賴人類疾病的動物模型是必須的。透過非侵入式且可重複在同一隻動物進行造影分析，除了減少研發成本同時可排出個體間的表現差異。相較於傳統實驗室犧牲實驗動物且依賴組織切片、組織學、組織化學或免疫組織化學染色的研究方法來評量，非侵入式分子造影可得到如組織學染色一樣的生物標記，包括反應的位置、大小程度甚至還能避免在不同的時間點犧牲大量動物才能追蹤不同時間之變化。小動物正子/電腦斷層掃描造影大大提升癌症診斷藥物開發的進展。癌症轉移是威脅病人存活最大的問題。由於胰臟癌會誘發腫瘤周遭組織纖維化包覆實質腫瘤，導致藥物治療在胰臟癌效果不佳，目前手術是唯一有機會治癒原位胰臟癌的方法。而進行胰臟癌手術的前提必須是沒有遠端轉移的發生。然根據統計，術前電腦斷層、核磁共振或正子攝影顯示無肝臟轉移的病人，卻在手術切除後平均三個月內發生肝臟轉移。對於在術後短時間內發生肝轉移，很可能是術前已有微小肝臟轉移發生而未被偵測到。隨著電子產業的進步，結合解剖與功能性影像的正子斷層掃描造影儀器在本世紀初獲得廣泛使用，影像融合技術提升醫學影像革命性發展，再加上分子生物科技的研究獲得重大突破，醫學檢測可透過標定(4S)-4-(3-18F-fluoropropyl)-l-glutamate (FSPG)特定正子藥劑，進行腫瘤特性分子影像的追蹤檢測與臨床應用，已被證實可偵測胰臟癌微小之肝臟轉移。由於胰臟癌具有大量依賴麩醯胺酸(Glutamine)的特殊代謝模式，其目的是藉由 xc-transporter (xCT)轉運蛋白活性來降低癌細胞體內大量累積的氧化壓力。FSPG 是 glutamine 類似物，正常肝臟其 xCT 活性低，不會攝取 FSPG，因此具有潛力用來偵測胰臟癌的肝轉移發生。目前 FSPG 檢測靈敏度在小動物正子掃描儀可達 1.2 mm，而在臨床用正子掃描儀則達 3.2 mm。手術本身在術後迅速發生肝轉移的病人不僅不能延長其壽命，反而讓他們承受了手術的風險與痛苦且耽誤了化療的時機。未來，利用 FSPG 正子造影掃描診斷胰臟癌微小肝轉移，不僅可提早發現肝轉移，更可避免不必要甚至有害的手術。