(12)

國內醫用迴旋加速器的建置與發展

Construction and Development of Medical Cyclotron in Taiwan

時　　間：112 年 7 月 8 日(星期六) 08:15~12:00
地　　點：臺北榮民總醫院 第三門診 9 樓創新沙龍

08:15-08:20	***Opening Remarks***	彭南靖副教授 Nan-Jing Peng
08:20-08:30	***貴賓致詞***	李偉強教授 Wui-Chiang Lee
	座長：黃文盛 教授 (Wen-Sheng Huang) 高潘福 教授 (Pan-Fu Kao)	
08:30-09:00	福島核電廠意外後，輻傷救護、社區復原與溝通之經驗分享 Experiences in Radiation Medicine and Risk Communication for Recovery of the Community in Fukushima after a Nuclear Disaster	高村昇教授 Noboru Takamura (日本)
09:00-09:30	溫哥華 BC Cancer 在 PSMA 核醫藥物的研發經驗 Development of Prostate-Specific Membrane Antigen-Targeted Radiopharmaceuticals for Diagnosis and Therapy of Prostate Cancer at BC Cancer	林國賢博士 Kuo-Shyan Lin (加拿大)
09:30-10:00	攝護腺癌正子檢查製劑之發展 Development of PET Radiopharmaceuticals for Imaging Prostate Cancer	魏孝萍副教授 Shiaw-Pyng Wey
10:00-10:20	***Coffee Break***	
	座長：王昱豐 副教授 (Yuh-Feng Wang) 高梓木 博士 (Tsu-Mu Kao)	
10:20-10:45	北榮正子藥物的供應及未來計劃 PET Radiopharmaceutical in TVGH: Retrospect and Prospect	張文議博士 Wen-Yi Chang
10:45-11:10	核能研究所核醫藥物研發現況與未來展望 Current Status and Future Prospects of Nuclear Medicine Research and Development at INER	樊修秀博士 Shiou-Shiow Farn
11:10-11:35	精準醫療之跨界思考－從產業界看台灣放射新藥開發 Cross-Border Thinking in Precision Medicine: Taiwan Radiopharmaceutical R&D from Academia to Industry	黃雅瑤博士 Ya-Yao Huang
11:35-12:00	核醫藥物生產及供應鏈的挑戰 Challenges in the Production and Supply Chain of Nuclear Medicine	林亮光總經理 Lian-Kwung Lin

Experiences in radiation medicine and risk communication for recovery of the community in Fukushima after a nuclear disaster

福島核電廠意外後，輻傷救護、社區復原與溝通之經驗分享

Noboru Takamura
高村昇
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Twelve years have passed since the accident at the Fukushima Daiichi Nuclear Power Station (FDNPS) in 2011. Since then, we have been assisting in reconstruction efforts for Kawauchi Village, Fukushima Prefecture, which was the first village to declare that residents could return to their hometown. In April 2013, Nagasaki University and the Kawauchi Government Office finalized an agreement of cooperation for reconstruction of the village. The university began comprehensive support for residents of the towns of Tomioka, Ohkuma, and Futaba in 2016, 2020, and 2021, respectively. Twelve years after the accident, gaps in the recovery process are apparent in all municipalities surrounding the FDNPS. After a nuclear disaster, radiation medical science experts need to fully understand the situation in each municipality in order to contribute most effectively to recovery.

Development of prostate-specific membrane antigen-targeted radiopharmaceuticals for diagnosis and therapy of prostate cancer at BC Cancer

溫哥華 BC Cancer 在 PSMA 核醫藥物的研發經驗

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Background: Prostate-specific membrane antigen (PSMA)-targeted radiotherapeutic agents have been widely used in the clinic to treat metastatic prostate cancer. However, their off-target uptake in kidneys and salivary glands poses a toxicity concern and can severely affect quality of life for survivors. Recently we observed in a mouse model that monosodium glutamate pretreatment reduced uptake of ^{68}Ga-PSMA-11 in salivary glands and kidneys but had no effect on tumor uptake (Rousseau E, et al. J Nucl Med 2018; 59: 1865). This suggests that the Glu motif in the widely used Lys-urea-Glu pharmacophore might mediate the off-target uptake of PSMA-targeted radioligands.

Methods: In this study, we investigated the effects of replacing Glu in the PSMA-targeted Lys-urea-Glu pharmacophore with a close analog on the uptake of kidneys, salivary glands and PSMA-expressing LNCaP tumor xenografts. New derivatives obtained by replacing Glu with Aad (2-aminoadipic acid), Cmc (S-carboxymethylcysteine), Cms (O-carboxymethylserine), or 4-F-Glu were synthesized and radiolabeled with ^{68}Ga or ^{18}F for positron emission tomography imaging in mice bearing LNCaP tumor xenografts.

Results: Compared with radioligands derived from the Lys-urea-Glu pharmacophore, the PSMA ligands derived from Lys-urea-Aad, Lys-urea-Cmc, Lys-urea-Cms and Lys-urea-4-F-Glu showed comparable uptake values in tumors but much lower uptake values in kidneys and salivary glands.

Conclusion: Our data suggest that replacing Glu in the widely used PSMA-targeted Lys-urea-Glu pharmacophore with a close analog can greatly reduce the off-target uptake in kidneys and salivary glands. The new pharmacophores, Lys-urea-Aad, Lys-urea-Cmc, Lys-urea-Cms and Lys-urea-4-F-Glu, are promising for the design of PSMA-targeted radioligands especially for radiotherapeutic agents to minimize toxicity to kidneys and salivary glands.

Developments of PET radiopharmaceuticals for imaging prostate cancer

攝護腺癌正子檢查製劑之發展

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Prostate cancer is the most common cancer diagnosis in men and a leading cause of cancer-related morbidity and mortality. Novel radiopharmaceuticals such as ^{18}F-fluciclovine and choline PET have been used increasingly in the biochemical recurrence (BCR) setting with limited specificity. The increasing use of radiopharmaceuticals that target the prostate-specific membrane antigen (PSMA) is based on growing scientific evidence that supports their favorable imaging performance. Many PSMA-targeted imaging agents are being evaluated, and two are currently approved by the Food and Drug Administration, USA: ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. Other tracers are being evaluated in phase III trials, including ^{18}F-PSMA-1007, ^{18}F-rhPSMA-7.3, ^{18}F-CTT1057, ^{68}Ga-PSMA-R2, and ^{64}Cu-SAR-bisPSMA. This presentation reviews the developments of these PET tracers particularly in radiochemical and industrial concerns.

PET radiopharmaceutical in TVGH: Retrospect and prospect

北榮正子藥物的供應及未來規劃

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The National PET/Cyclotron Center (NPCC) of Taipei Veterans General Hospital (TVGH) was completed at the end of 1992 and run by the Nuclear Medicine Department. The facility continues a long legacy of radiochemistry work that started in 1993 with the installation of the first medical base cyclotron in Taiwan, a Scanditronix MC17. The machine has proton source and is currently outfitted with 5 targets (^{18}F-, ^{18}F2, ^{11}C, ^{13}N and ^{15}O).

NPCC has two missions: a clinical production laboratory where the radiopharmaceuticals used in routine diagnostic scans, and a clinical studies production for research. NPCC produce F-18 FDG, F-18 NaF, N-13 NH3 and C-11 sodium acetate for clinical used (TFDA approved). NPCC also produce F-18 PSMA1007, F-18 FEPPA, F-18 Fallypride, F-18 FHBG, F-18 FAHA and C-11 PIB for human clinical trials.

The clinical production laboratory is operated under cGMP regulation. The facility currently has two dispensing isolator, four mini hot cells. Two of the mini hot cells house two NEPTIS boxes (mosaic-RS and perform) that are dedicated to daily F-18 FDG production. In addition, there are two Eckert & Ziegler synthesis modules for nucleophilic fluorination and C-11 label radiopharmaceuticals (C-11 sodium acetate).

Scanditronix MC17 was used almost 30 years, some component of the cyclotron maybe hard to get for maintenance. That machine is not able to production new isotope (ex. Ga-68, Cu-64 and Zr-89) for current radiopharmaceuticals.

In the future, we will setup new cyclotron for several isotope production (ex. Ga-68, Cu-64 and Zr-89). Moreover, some prospects of research and development of radiopharmaceuticals in the near future are discussed.

Current status and future prospects of nuclear medicine research and development at INER

核能研究所核醫藥物研發現況與未來展望

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樊修秀

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行政院原子能委員會核能研究所 同位素應用組

With the advent of the era of precision medicine, diagnostic and therapeutic molecular imaging technology or drugs play an indispensable role. The Institute of Nuclear Energy Research (INER) has been committed to the research of nuclear medicine and the development of imaging technology for many years. In addition to having a one-stop nuclear medicine development industry chain (from innovative research to commercialization), it is more active in line with the global trend of precision medicine development, launching a new generation of cyclotron construction plan.

So far, special achievements include: (1) Stable supply of "INER Thallium Chloride (Thallium-201) Injection" for routine clinical use. (2) Completion of pre-clinical biological research, establishment of automatic synthesis process production system and 3 batches of trial production of "Long-acting Nuclear Medicine Lu-177-PSMA INER-56 Targeted Therapy for Prostate Cancer", (3) Extended the drug stability of "I-123-MIBG injection" to 10 hours (originally 6 hours), and was approved by TFDA on May 24, 2011, and officially supplied to hospitals for academic clinical trials. (4) Continuing to implement the phase II clinical trial of "INER DOLACGA imaging agent for Liver Function", because it has excellent liver target properties and can be used to evaluate liver function and liver disease progression. (5) Taiwan's first "Carbon-14 Label Metabolism Platform" has obtained GLP certification and TFDA registration, which can accelerate the development and marketing of new drugs in the domestic industry, academia and medical circles. (6) The "*In vivo* Molecular Imaging" and "Biodistribution" test items of the "Molecular Imaging and Radiopharmacology Laboratory" have passed TAF ISO/IEC 17025 certification. (7) The only "Radiation Toxicology Laboratory" in Taiwan that has passed GLP certification, providing certified quality and safety data to accelerate the development of new nuclear medicine drugs. (8) "National Neutron and Proton Science Applied Research - 70 MeV Medium Cyclotron Construction Project", a four-year project (2023-2026), was approved by the Executive Yuan on October 21, 2010, and it has been officially launched and implemented this year.

Finally, INER looks forward to working hand in hand with the industry-university-research-medicine community in the future to march towards a new era of precision medicine in nuclear medicine.

Cross-border thinking in precision medicine: Taiwan radiopharmaceutical R&D from academia to industry

精準醫療之跨界思考：從產業界看台灣放射新藥開發

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In order to create a new future for Taiwan healthcare with radiopharmaceuticals that we know much, I was founded Primo Biotechnology (Primo) in 2021. The vision of Primo is to facilitate the accessibility of novel RPs to advance Taiwan healthcare. With a full line of radiochemistry systems and PIC/S GMP-compliant manufacturing to supply novel agents for diagnosis and therapy, Primo will dedicated to deliver the next generation of personalized and precision healthcare solutions to help people in need, especially the emerging therapeutic strategy, radioligand therapy (RLT). In this talk, the different thinking working in an academic institution and a pharmaceutical company about radiopharmaceutical development will be shared via personal 20-year R&D journey and recent career change.

In addition, Asia has been a rising player in terms of economic development and so the status of Asia radiopharmaceutical market does. However, due to various barriers such as the geographical environment and transportation, Asian countries encounter challenges in information exchange and medicine delivery, not to mention differences in language, cultures, and regulations. Not only for radiopharmaceutical market, but the development of novel radiopharmaceuticals in Asia still faces considerable levels of difficulty and challenges to overcome. Taiwan has been recently regarded as an important base in Asia-Pacific economic tactics and Taiwan will be highly potential to be a great model to overcome these existing challenges through building a unique Taiwan academia-industry collaborative model. Consequently, based on personal observation for the current status of Taiwan hospitals and radiopharmaceutical companies, several trends of Taiwan radiopharmaceutical development will be suggested and Taiwan academia-industry collaborative models for radiopharmaceutical development also will be proposed, which may will be a win-win key for Taiwan healthcare.

Challenges in the production and supply chain of nuclear medicine

核醫藥物生產及供應鏈的挑戰

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Nuclear medicine is not only a drug management, but also category a radioactive substance, which can be described as the blessing of double regulations. The level of regulatory supervision is probably incomparable except for weapons and ammunition. The direct competent authorities include the Ministry of Health and Welfare(TFDA) and the Atomic Energy Council at the central level, and local health bureaus and environmental protection bureaus at the local level. Under the current PIC/S GMP standard, other raw materials other than the main ingredients must have GMP certification in addition of Certificate of Analysis. Various quality control operations in the pharmaceutical production process also include various validation operations. The finished pharmaceutical product still needs to comply with the GDP delivery specification. From the core indicators of GMP pharmaceutical factories: air flow, water flow, material flow and human flow, to the final industrial waste treatment with or without radiation, all aspects are different from ordinary drugs.

Because it is a radiopharmaceutical, it is a competition with time and cost from the qualification of the direct front-line production personnel to the qualification of the transport personnel, the use of equipment, half-life, and road supervision. Medical institutions that are end-users are also subject to dual regulations, and they also have various issues such as compliance personnel, exposure, equipment costs, and operating costs.

In detail, there are at least 50 regulations and orders layered on the nuclear medicine pharmaceutical industry and nuclear medicine department. Under the premise of abiding by laws and regulations, nuclear medicine has technical thresholds and cost thresholds that cannot be compared with other departments.

Today we are going to talk about how the nuclear medicine pharmaceutical industry and the clinical nuclear medicine team can improve the accessibility of nuclear medicine in various difficulties.