

出國報告（出國類別：其他）

出席第 23 屆歐洲核醫學國際會議公差 報告

服務機關：核能研究所

姓名職稱：樊修秀
林武智

派赴國家：奧地利維也納

出國期間：99 年 10 月 7 日~99 年 10 月 15 日

報告日期：99 年 11 月 9 日

摘要

歐洲核醫學會 (European Association of Nuclear Medicine; 簡稱EANM) 每年輪流在歐洲各會員國舉辦國際性「歐洲核醫學年會」, 為全球核醫學高階創新與新技術發展之指標會議之一, 邀集產、官、學、研界提出相關論文, 以促進核醫藥物相關領域科技研發、技術創新及商業模式之互動與合作。第23屆歐洲核醫學年會(23rd EANM)在奧地利維也納會展中心ACV (Austria Center Vienna)舉行。會議主席由維也納聖文森醫院核子醫學部PET/CT中心 (St Vincent's Hospital PET/CT Center LINZ, Nuclear Medicine & Endocrinology) Werner Langsteger教授擔任, 會期於2010年10月9日起至10月13日止, 為期五天。

本年度本所共7篇壁報論文獲大會接受展示。職 修秀與林組長出席23rd歐洲核醫學年會與發表論文, 收集歐洲核醫相關研究之最新發展與明瞭未來發展趨勢, 作為未來計畫研發方向以及策略規劃參考。本次與會聆聽專業的演講或是訓練課程, 包括從臨床觀點來看PET正子藥物應用於缺血性心臟病診斷、核醫藥物應用在評估心臟代謝功能、個人化之分子影像藥物開發、分子影像藥物: 診斷性PET正子藥物研製與標靶治療核醫藥物研製、學術研究到產業應用的成功故事、拜耳先靈西藥部 (BSP) 發展願景到核醫藥物與相關儀器之展示資訊等, 其目的在於了解國外發展現況與趨勢, 以作為本所立足於核醫藥物研發領域之先探。

目前對於疾病的探索與藥物開發, 努力導向在分子層次, 本所開發的分子影像核醫藥物, 可以觀察細胞與分子層次之活體組織生物反應過程、藉由極微量濃度之分子影像藥物來觀察接受體與基因表現, 無庸置疑, 分子影像藥物逐漸扮演舉足輕重的角色。FDA (USA) 於2006公告eIND規範內容, 導致諸多相關於心臟血管、神經學科學以及腫瘤醫學之candidate drugs 設計選擇及開發如雨後春筍而繁茂。多年來本組努力於開發診斷性核醫藥物, 獲得多項本國食品藥物管理局 (TFDA) 藥物許可證, 並同步供應全國醫學中心及各級醫院臨床使用, 且持續進行多項人體臨床試驗, 目前, 也逐漸趨向治療性核醫藥物之開發。

綜觀23rd EANM, 學術研究單位、製藥公司與醫院之合作關係, 採取團隊合作的策略聯盟, 研發速度快且精準, 無非是希望能挑選具有疾病診斷與治療應用價值之核醫藥物後, 成功推向商品化產品, 對本所核醫藥物開發與研發計畫方向提供極具參考價值之長遠規劃與思維。

本次除參與 23rd EANM 以及非正式拜訪駐奧地利_台北經濟與文化代表處, 討論有關本國核能發展方向及重要性、本國參與 IAEA 國際組織業務與關聯性、介紹本所開發核醫藥物之應用價值及目前對醫學診療之貢獻價值、再生能源之開發應用價值等, 開闊國際視野與增廣相關見聞。

目 次

頁次

摘 要	i
一、目 的	1
二、過 程	3
(一) 行程	3
(二) 23 rd EANM簡介	7
(三) 23 rd EANM Highlight lectures	8
(四) PET正子藥物於缺血性心臟病診斷之臨床觀點	12
(五) 核醫藥物如何評估心臟代謝功能	13
(六) 個人化之分子影像藥物開發	14
(七) 分子影像藥物：診斷性PET正子藥物研製	16
(八) 分子影像藥物：標靶治療核醫藥物研製	17
(九) 從學術研究到產業應用的成功故事	19
(十) 拜耳先靈西藥部 (BSP) 發展願景	20
(十一) 核醫藥物與相關儀器之展示資訊	23
(十二) 拜訪駐奧地利_台北經濟與文化代表處	25
三、心 得	26
四、建議事項	27
(一) 建立靈長類動物實驗中心	27
(二) 診斷性核醫藥物研製：進行PET正子新藥物研製	27
(三) 標靶治療核醫藥物研製：進行生理作用機轉研究探討	27
(四) 研製正子藥物快速合成設備	27
(五) 積極與著名學術單位合作，尋求candidate新藥物	27
(六) 積極參與國際研討會，尋求合作契機與確立研發方向	27
五、附 錄	28

圖 目 錄

	頁次
圖一、奧地利維也納會展中心 ACV (Austria Center Vienna)	4
圖二、第 23 屆歐洲核醫學年會(23 rd EANM)會場指示圖	4
圖三、第 23 屆歐洲核醫學年會(23 rd EANM)場次展示牆	5
圖四、EANM 會場合影留念	5
圖五、本所 POSTER 壁報展示 (六篇)	6
圖六、奧地利_台北經濟與文化代表處合影留念	25

表 目 錄

	頁次
表一、參加 23 rd EANM_本所發表核醫研究論文統計表	1
表二、參加 23 rd EANM_行程與工作重點	3
表三、Highlight Lectures	8
表四、GE、Siemens、Lantheus、BSP 與 MIP 等公司進行的臨床試驗 (phase I,II,III)	16

一、目的

核能研究所(以下稱為本所)正積極開發新型診斷與治療用核醫藥物等，為瞭解先進國家在核醫藥方面技術開發現況與未來市場拓展之規劃，並建立與歐盟核醫專家及我國駐外專家之溝通與資訊交換管道，本所同位素應用組林組長武智率領核醫製藥中心品管負責人暨「核醫藥物檢驗品質管制」計畫主持人樊修秀小姐參加歐洲核醫年會，對本所未來核醫藥物相關計畫策略規劃之資訊搜集有所助益。本年度本所共7篇壁報論文獲大會接受，林組長武智與樊修秀小姐同時亦將代表本所在年會上發表6篇核醫研究論文(論文統計如表一，論文內容請參閱附錄一)，將我國在核醫方向之努力與研發成果向國際社會介紹與展示，期盼能藉此機會瞭解國外學者之觀點及建議並且提升我國核醫在歐洲地區之交流機會與影響力，以朝國際化的方向努力。

表一、參加 23rd EANM_本所發表核醫研究論文統計表

序號	作者	論著名稱	壁報展示類別
1	李銘忻 林金陣 戴以禮 丁澤錚 林武智	An organic-resin generator for ⁶⁸ Ga-PET labelling	Poster Number: TP63 Session: TP3 - Technologist Poster Session 3
2	李銘忻 林武智	An architectural innovation for Ga-68-DOTATOC radiopharmaceuticals automatic dispensing system	Poster Number: TP53 Session: TP3 - Technologist Poster Session 3
3	李銘忻 林武智 林金陣 戴以禮 丁澤錚	Simple, fast preparation of gallium chloride from the Ga-67-citrate injection	Poster Number: TP23 Session: TP2 - Technologist Poster Session 2
4	李銘忻 杜定賢 林金陣 丁澤錚 林武智	Assessment of irradiation parameters for Ga-68/Ge-68 generator	Poster Number: TP15 Session: TP1 - Technologist Poster Session 1
5	許晉瑋	Comparative Therapeutic Efficacy of ¹⁸⁸ Re-Liposomes and 5-FU in LS-174T human Colon Carcinoma Solid Tumor Xenografts	Poster Number: PW02 Poster Session: Poster walking tour 2

6	劉技謀	Evaluation of Acute Toxicity of 188Re-BMEDA-liposome in Rats	Poster Number: 18 Poster Session: P14
7*	夏建忠	The Comparative Study of BnAO-derivative on Hypoxic Model Imaging and Assess the Effect of Pentoxifylline	Poster Number: 1 Poster Session: P14

Note: “*”該作者本次未提供壁報。

本次國外公差之主要目的有三：

1. 代表本所於23rd EANM發表6篇核醫相關研究論文。
2. 積極參與23rd EANM，學習最新核醫發展新知，並探知合作對象。
3. 積極參與23rd EANM，提升本所國際能見度，並尋求藥物研發新契機。

二、過 程

(一) 行程

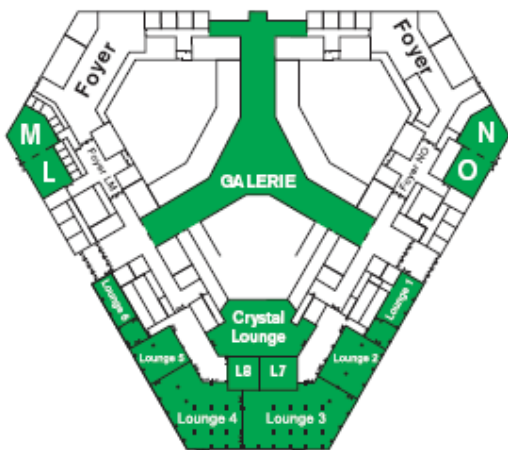
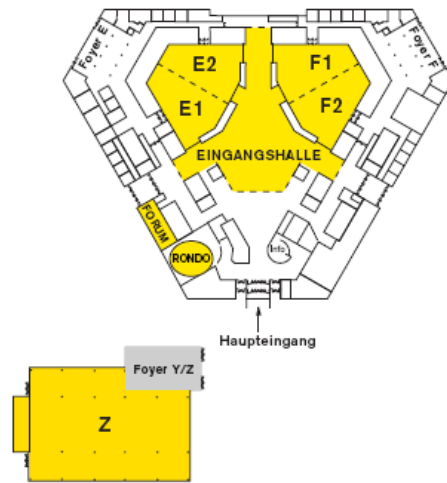
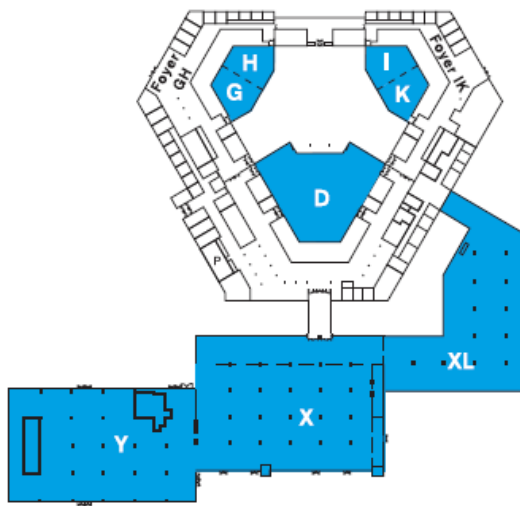
今年第23屆歐洲核醫學年會(23rd EANM)在奧地利維也納ACV舉行，維也納為奧地利之首都，共有兩百多萬人口，位於奧地利東北部阿爾卑斯山北麓維也納盆地之多瑙河邊，為歐洲最古老大學城市之一，醫藥、藝術、人文及音樂頗負盛名。本次公差自99年10月07日至99年10月15日共計9天，扣除飛機行程之來往，實際工作共5天，工作內容重點如下表二。會場指示圖如圖1及圖2：

表二、參加 23rd EANM_行程與工作重點

日 期	工 作 重 點
99/ 10/ 07 ~ 99 / 10/ 08	去程: 台灣桃園國際機場(TPE)—維也納國際機場(VIE)
99/ 10/ 09 ~ 99/ 10/ 13	<ol style="list-style-type: none">1. 參加第 23 屆歐洲核醫學年會(23rd EANM)，張貼本所壁報論文 6 篇，聆聽基礎與研發創新之 seminar，研讀並拍照重要的 posters，參觀儀器設施與藥物展示，討論核醫藥物最新進展。(議程請參閱附錄二)。2. 參訪駐奧地利代表處。
99/ 10/ 14 ~ 99/ 10/ 15	返程: 維也納國際機場(VIE)—阿姆斯特丹機場(AMS) —台灣桃園國際機場(TPE)



圖一、奧地利維也納會展中心 ACV (Austria Center Vienna)



圖二、第 23 屆歐洲核醫學年會(23rd EANM)會場指示圖

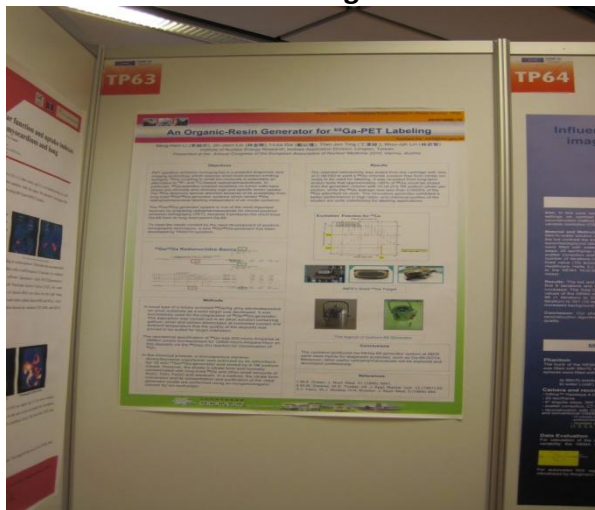


圖三、第 23 屆歐洲核醫學年會(23rd EANM)場次展示牆



圖四、EANM 會場合影留念：本所同位素應用組組長_林武智博士、台灣核醫學會理事長暨成大醫院核醫部主任_姚維仁醫師、三軍總醫院核醫部主治醫師_黃文盛醫師、國防醫學院生物及解剖科研究所_馬國興副教授以及三軍總醫院核醫部[製藥組]_彭敬成主任、新光醫院主治醫師_沈業友醫師與職 修秀合影留念於 23rd EANM 會場

1. An organic-resin generator for ^{68}Ga -PET labelling



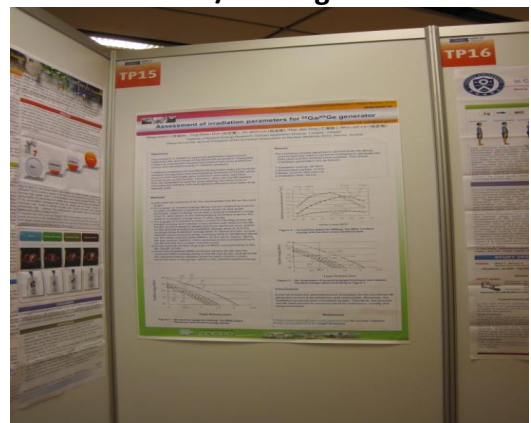
2. An architectural innovation for Ga-68-DOTATOC radiopharmaceuticals automatic dispensing system



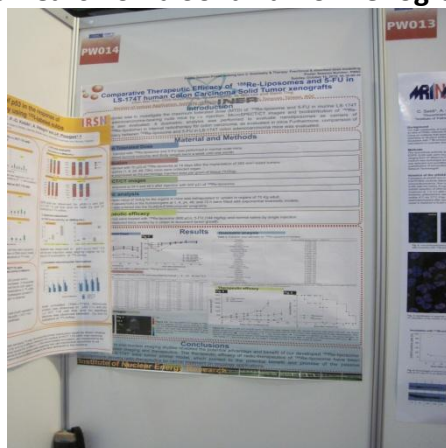
3. Simple, fast preparation of gallium chloride from the Ga-67-citrate injection



4. Assessment of irradiation parameters for Ga-68/Ge-68 generator



5. Comparative Therapeutic Efficacy of ^{188}Re -Liposomes and 5-FU in LS-174T human Colon Carcinoma Solid Tumor Xenografts



6. Evaluation of Acute Toxicity of ^{188}Re -BMEDA-liposome in Rats



圖五、本所 POSTER 壁報展示 (六篇)

(二) 23rd EANM 簡介

歐洲核醫學會(European Association of Nuclear Medicine；簡稱 EANM) 每年輪流在歐洲各會員國舉辦國際性「歐洲核醫學年會」，為全球核醫學高階創新與新技術發展之指標會議，邀集產、官、學、研界提出相關論文，以促進核醫藥物相關領域科技研發、技術創新及商業模式之互動與合作。

23rd EANM在奧地利維也納會展中心ACV (Austria Center Vienna)舉行。會議主席由維也納聖文森醫院核子醫學部PET/CT中心 (St Vincent's Hospital PET/CT Center LINZ, Nuclear Medicine & Endocrinology) Werner Langsteger教授擔任，會期於2010年10月9日起至10月13日止，為期五天，由歐洲核醫學會 (包括科學組與技術組委員會)、維也納當地核醫學會與歐洲科學委員會共同主辦，議程內容專注於現行核醫藥物發展與未來發展，並與相關先進技術協會緊密結合，呈現核子醫學多種技術之知識密集面向。23rd EANM在會議主題自新藥物開發、基礎研究、臨床技術、數據分析、案例互動交流、診斷性核醫藥物、治療性核醫藥物到新穎儀器發展等領域主題，各項主題納入於Scientific Programme 【細分成Oral Sessions(口頭報告)、Plenary Sessions (全員大會講座)、Poster Presentation (壁報展示)、Poster Walk (步行式壁報報告)、Symposia (座談會)】、Technologists' Programme (Oral Sessions & Poster Presentation)、CME Programme (繼續教育課程[醫學]；Oral Sessions)、CTE Programme (繼續教育課程[技術]；Oral Sessions) 等四大類程序表進行討論，以掌握藥物與儀器研發現況及未來之趨勢。所有場次與受邀講者人數如下表。

VIENNA'10 SESSION BREAKDOWN	
PLENARIES-SYMPOSIA-CME SESSIONS	30
INVITED SPEAKERS	94
PLENARIES	4
INVITED SPEAKERS	10
SYMPOSIA	13
INVITED SPEAKERS	45
CME SESSIONS	13
INVITED SPEAKERS	39
SCIENTIFIC SESSIONS	140
FEATURED SESSIONS	11
ORAL SESSIONS	55
POSTER WALK SESSIONS	10
POSTER SESSIONS	64

(三) 23rd EANM Highlight lectures

23rd EANM由來自全球57個國家踴躍投稿，其各國投稿百分比多半以歐盟國家為主，其他亞洲地區如日本(7%)與韓國(3%)亦積極參與，最值得一提的是已見到中國大陸的積極參與。以[規模]來說，超過5,000名核子醫學科醫師、研究學者與技術人員共同參與及3,200m²的展覽場地，展覽場地共分為三處，一為供廠商展示最新核醫藥物與儀器進展，其餘二處均為壁報展示，今年最特別的是技術類壁報為一獨立展場。以[科學領域]來說，刊載1,703篇摘要，包括腫瘤(40%)、基礎核子醫學(21%)、放射性示蹤劑(11%)、神經學與精神科學(10%)、心臟血管(9%)、影像醫學儀器與數據分析(9%)等六大研究領域。以[專業領域]來說；多達100場以上的演講場次與超過40場次之繼續教育訓練課程(Continuous Medical Education；CME)。

演講內容主要著重在三方面：

- (1) Oncology方面：主要偏重在肺癌(15%)、消化道(13%)、內分泌與神經內分泌(12%)、治療評估(10%)等。
- (2) Neurology & Psychiatry方面：以接受體或轉運體造影研究(35%)、臨床神經學研究(31%)、阿茲海默氏症(Alzheimer's disease；AD)或輕度認知障礙研究(mild cognitive impairment；MCI)(16%)等為主。
- (4) Therapy方面：以治療效用評估研究(40%)、放射治療研究(30%)、放射免疫與接受體治療研究(18%)等為主。

無論是口頭報告或是壁報展示[包括儀器技術類、臨床前研究類或是臨床研究類]，本次被大會專家學者所選取出來之卓越顯著研究報告，如表三。

表三、Highlight Lectures

Highlight Lectures		
ONCOLOGY		
1 OP228	¹⁸ F-FDG PET/CT and diagnostic CT for the prediction of histopathologic treatment response after EGFR-TK1 treatment in patients with resectable NSCLC	TS. Aukema
2 OP344	Radiofrequency Ablation in Lung Cancer: comparison between contrast-enhanced CT and PET/CT	G.Capriotti
3 OP027	The value of Parametric F-18-FDG-PET Images for the Detection of Liver Metastases in Patients with Gastrointestinal Stromal Tumors Under Anti-proliferative and Anti-angiogenic Therapy	D.J.Apostolopoulos
4 OP154	Role of FDG PET-CT in HTT treatment planning for patients with locally advanced pancreatic cancer: selection and treatment monitoring	Maria Picchio
5 OP392	Immunohistochemical Validation of Somatostatin-Receptor PET/CT As In-Vivo Method For Quantification of Receptor Density On Neuroendocrine Tumors	Luisa Goetze
6 OP557	Impact of PET/CT with FDG on the clinical management of patients with ovarian cancer	D.Volterrani
7 OP585	Total ¹⁸ F-FDOPA Tumor Uptake Reflects Metabolic Endocrine Tumor Activity in patients with a Carcinoid Tumor	HB Fiebrich
8 OP586	Comparison of FDOPA(¹⁸ F) and DOTATOC (⁶⁸ Ga) PET/CT for detection of ileal carcinoid tumors	F.Montravers

9 OP343	Assessment of Tumor Volume in Lung Cancer: PET versus CT based Methods	Patsuree Cheebsumon
10 OP222	Impact on treatment using PET/CT for radiotherapy planning	CB Christensen
11 OP223	Prospective study on the role of ¹⁸ F-FDG PET/CT on planning of the radiotherapy with elective nodal irradiation (ENI) for non-small cell lung cancer	M. Kolodziejczyk
12 PW031	Usefulness of 4D PET/CT imaging in lung lesions with respiratory gated scan	S. Jinnouchi
13 OP470	Imaging Assessment of FDG-avid lymphomas. Is Diagnostic CT a necessary adjunct to PET-CT?	M.Sami
14 OP101	Meta-analysis of progression-free survival upon interim FDG PET results during first line chemotherapy in Hodgkin's Disease (HD).	S.N.F.Rizvi
15 OP471	FDG-PET for diagnosing bone marrow involvement in children and adolescents with Hodgkin's lymphoma	R.Kluge
16 OP113	Metabolic Tumor Volume Assessment by ¹⁸ F-FDG PET/CT in the Evaluation of Plasma Cell Mass and Prediction of Outcome in Patients with Multiple Myeloma	R.Fonti
17 TP19	Evaluation of Treatment Response using Whole Body metabolic Tumor Burden (WBMTB) Estimated by ¹⁸ F-FDG PET/CT Imagings in Paediatric Lymphoma	A.Guapta
18 OP468	Evaluation of Initial ¹⁸ F-FLT-uptake for Prediction of Survival in Patients with Aggressive Non-Hodgkin's Lymphoma (NHL) Undergoing R-CHOP Treatment	Ken HerrmannF
19 OP230	Final Results of a Phase I/II Trial of Fractionated Radioimmunotherapy (RAIT) with anti-CD22 ⁹⁰ Y Epratuzumab Tetraxetan in Released/Refractory Non-Hodgkin Lymphoma	D.M.Goldenberg
20 OP411	Usefulness of ¹¹ C-Choline PET/CT as a First Diagnostic Procedure in Patients with Biochemical Relapse and PSA Level Lower than 1.5 ng/mL	C.Fuccio
21 OP552	Inhibition of Human Prostate Cancer Grown by Targeting Prostate Specific membrane Antigen (PSMA) using an I-131 Labeled Small molecule Inhibitor	SM Hillier
THE BREAST		
1 OP226	Assessment of Response after two cycles of neoadjuvant chemotherapy in Locally Advanced Breast Cancer Using FDG PET/CT	D Groheux
2 T15	Dedicated Mini PET System for Breast Screening; A Technologists Perspective	C.Vroonland
3 PW061	Molecular Breast Imaging (MBI) with a high resolution dedicated breast camera (DBC) in the detection of ductal carcinoma in situ (DCIS) a correlation with mammography (Mx) and histologic subtype	A.Spanu
THE THYROID		
1 OP022	Detection of thyroid remnant tissue and lymph node metastases with iodine-124 in DTC: PET alone vs. fused PET/MR vs. Integrated PET/CT	J.Nagarajah
2 OP103	⁶⁸ Ga-DOTA-Tyr ³ -Octreotide PET in thyroid cancer patients compared to ¹⁸ F-FDG PET and radioiodine Activity	Putzer D
3 PW040	Spontaneous course of disease in pediatric patients with thyroid cancer and pulmonary metastases after incomplete elimination of the metastases by high-dose radioiodine therapy: Results of a ten-year-follow-up	J.Biko
THE HEART		
1 T03	How to improve gated-SPECT myocardial perfusion using a high resolution matrix and scatter correction: preliminary results	A.Ghilardi
2 OP034	XPRESS3 Half-Dose/Half-Time Gated Cardiac SPECT Validation	G. Cantinho
3	Impact of attenuation correction in G-SPECT myocardial perfusion Imaging	D.Gencvesi

P203	Interpretation: results of the Multicenter SPAG (SPECT Attenuation-correction vs Gated) study	
4 OP158	Coronary Microvascular Dysfunction in Hypertrophic Cardiomyopathy is Related to Contractile Dysfunction Independent from Myocardial Injury: a PET and CMR study	S.A.J.Timmer
5 OP157	Effects of Alcohol Septal Ablation on Coronary Microvascular Function and Myocardial Energetics in Hypertrophic Obstructive Cardiomyopathy	S.A.J.Timmer
6 OP583	Incremental Prognostic Value of Myocardial Blood Flow Quantification with RB-82 Cardiac PET in Patients with Known or Suspected CAD	H.Farhad
7 OP420	Role of SPECT Imaging Over Clinical Data in the Definition of Likelihood of Coronary Artery Disease in Diabetic Patients	L.Evangelista
8 OP418	Impact of Inducible ischemia by SPECT Imaging on Cardiac Risk Assessment in Diabetic Patients: Results of a Prospective, Multicenter Trial	W.Acampa
9 OP579	Myocardial perfusion Scintigraphy 2008 in Germany- Results of the 4 th Query-	O.Lindner
NEUROLOGY AND PSYCHIATRY		
1 OP353	Resting-state brain metabolic connectivity in amnesic MCI-AD converters and healthy controls. A joint project of the European Alzheimer's Disease Consortium (EADC).	S.Morbelli
2 OP221	Phase 1 trials on florbetaben b-amyloid brain PET in elderly normal controls-Influence of ethnic group, age, gender, and tracer mass dose	Henryk Barthel
3 OP354	Results of a Multicenter phase 2 Trial to test Florbetaben for b-Amyloid Brain PET in Alzheimer's Disease	Osama Sabri
4 OP052	Fluorine-18 Labeled PET Probes for Imaging of Neurofibrillary Tangles	S.Furumoto
5 OP120	Correlations between striatal dopamine transporter (DAT) availability and psychiatric symptoms in movement diseases: A ¹²³ I-EP-CIT-Study	D.Digiuda
6 OP437	Predictive value of ¹²³ I-PE21 SPECT DAT Imaging with early signs of parkinsonism- a prospective study of 288 patients	Morten Ziebell
7 OP122	Cortical hypometabolism in untreated de novo Parkinson's disease: comparison of different normalization procedures	V Berti
8 OP440	ENCDAT-European Database of ¹²³ I-FP-CIT SPECT Scans of Healthy Subjects: Final Results	K. Tatsch
9 OP066	Imaging of Herpes Virus activity in the central nervous system of schizophrenic patients	J.Doorduyn
10 OP125	Feasibility of ⁶² Cu-ATSM PET to delineate misery perfusion in patients with major cerebral arterial occlusive lesions.	Hidehiko Okazawa
11 OP055	¹¹ C-AZ11696415: Characterization of a novel PET radioligand for in-vivo visualization of the mGlu5 receptor in the cynomolgus monkey brain	J.D.Aandersson
12 OP054	Synthesis and preliminary biological evaluation of ¹¹ C-MP10 and its region-isomer as potential radioligands for positron emission tomography imaging of phosphodiesterase-10A in the brain	M.Ooms
IMAGE PROCESSING AND INSTRUMENTS		
1 OP362	Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous tumor FDG uptake in PET studies	Floris H.P. van Velden
2 OP546	Optimization of Acquisition Time for Ultrafast Parathyroid SPECT Imaging Using a Solid State CZT Camera	J.A.Kennedy
3 OP133	The effect of MR radiofrequency coils on PET quantification in whole-body PET/MR: Results from a pseudo PET/MR phantom study	T Beyer
4 OP130	Innovative technologies for simultaneous TOF PET/MR	V.Schulz
5	Clinical application of whole-body hybrid PET-MR scanner in oncology	O.Ratib

OP134		
NEW TRACERS		
1 OP174	^{99m} Tc SAR-G1: A new candidate for GRPR-Targeted Tumor Imaging	Marsouvanidis PJ
2 OP308	Comparison of 68Ga labeled RGD-peptides for Imaging Integrin v 3 expression	P.Knetsch
3 OP177	A Novel ¹²³ I-Cubane labeled bombesin for Imaging GRP Receptor-Expressing Prostate Cancer Diagnosis	Z Yu
4 OP614	In vivo visualization of Transplanted islets in rat by SPECT with ¹¹¹ In-Exendin-3	Karolina Andralojc
5 P124	In vivo evaluation of carbon-11-labeled N-((S)-1-((S)-methylpiperidin-2-yl)ethyl)acetamide derivatives as a potential radioligands for glycine transporter 1	J Toyohara
THERAPY		
1 OP270	Multi scale approach for absorbed calculations in targeted radionuclide therapy	A.M.Govignon
2 OP373	The significance of Bremsstrahlung SPECT-CT of the Abdomen after Yttrium-90 microsphere selective internal radiation treatment (SIRT) in the early diagnosis of SIRT-induced extrahepatic side effects.	Hojjat Ahmadzadehfar
3 OP391	Upper-selective hepatic Arterial Infusion of Y-90-DOTA-TOC and / or Lu-177-DOTA-TATE in Neuroendocrine Liver Metastases after selective catheterization of the hepatic artery and permanent port installation, previously treated with high doses of In-111-DTPA-Phe1-octreotide	K.papakonstantinou
4 OP393	Peptide receptor radionuclide therapy with ¹⁷⁷ Lu-DOTATATE: the IEO phase I-II study	Lisa Bodei
5 OP457	European multicentre evaluation of radioembolisation with ⁹⁰ Y-labelled resin microspheres: an analysis of safety and predictors for survival in hepatocellular carcinoma (HCC)	J Arbizu
6 OP474	Nanovectorized internal radiation therapy in a glioblastoma rat model	C. Vanpouille
7 P175	Assessment of effectiveness and toxicity of the therapy with somatostatin analogue labeled ⁹⁰ Y-DOTATATE in patients with non-functional pancreatic neuroendocrine tumors (PNT)	A. Sowa-Staszczak

[代碼註記：OP: Oral Presentation，PW: Poster Walks，P: Poster Presentations，TP: Technologist Abstracts]

從 Highlight lectures 可知：

(一) oncology 方面：諸多基礎與臨床研究正如火如荼的進行、PET/CT 提供極佳預後病程評估、大量的臨床數據佐證 PET 應用的價值，特別是搭配其他診斷工具、臨床試驗量持續增加。

(二) Cardiovascular 方面：目前研究趨勢朝向多元化發展，包括技術持續進步、極佳的 PET 影像定量訊息的臨床應用、心臟影像臨床研究數據來提供病患疾病及預後管理以及臨床應用研究數量相當穩定。

(三) Neurology and Psychiatry 方面：進行多項的基礎與臨床研究、PET 提供 Alzheimer's disease 有力診斷評估工具、SPECT 與 PET 臨床數據證實在運動失調的診斷價值等。

結語：PET/CT 應用在癌症治療評估的衝擊研究 (Impact study) 持續增長、治療性核醫藥物研究快速增加、基礎與臨床研究多偏重在 oncology 與 neurosciences，此外並發展出 PET/MR 新技術。

(四) PET 正子藥物於缺血性心臟病診斷之臨床觀點

PET 正子藥物於缺血性心臟病 (ischemic heart disease) 診斷之心肌灌注掃描檢查之核醫藥物很多，例如： $[^{13}\text{N}]\text{NH}_4^+$ 、 $[^{15}\text{O}]\text{H}_2\text{O}$ 、 $[^{18}\text{F}]$ -labelled compounds 以及目前本所已穩定供應之「核研氯化亞鉍注射劑， $[^{201}\text{Tl}]\text{TlCl}$ 」與「美必鎔心臟造影劑，MIBI」等。此外，早於 1992，Sr-82/Rb-82 generator 是第一個得到美國 FDA 核准使用於心肌灌注掃描檢查之 PET 正子藥物。

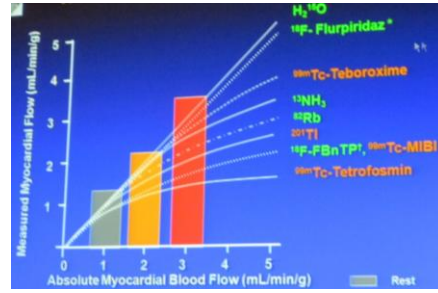
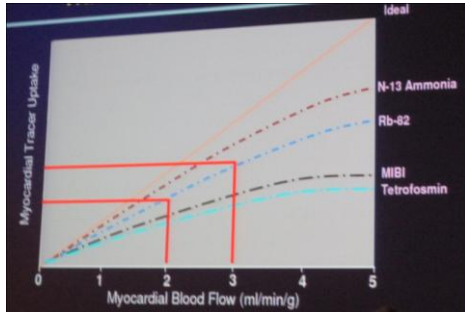
FDA-Approved PET Radiopharmaceuticals					
Radiopharmaceutical	FDA Approval of Clinical Utility		NDA Approval		
	Year	Indication	Year	Number	Manufacturer/Applicant
$[^{18}\text{F}]\text{Fluoride}^*$	1972	Bone imaging	1972	17-042	New England Nuclear
^{82}Rb -generator	1992	Myocardial perfusion	1989	19-414	Squibb Diagnostics
$[^{18}\text{F}]\text{FDG}$	1994	Epileptic foci	1994	20-306	Methodist Medical and CTI, Peoria, IL
$[^{18}\text{F}]\text{Fluoride}$	2000	Bone Imaging			
$[^{13}\text{N}]\text{NH}_4^+$	2000	Myocardial perfusion			
$[^{18}\text{F}]\text{FDG}$	2000	Epileptic foci in brain	2004	70-638	WMCCU, New York
		Myocardial glucose metabolism	2005	21-870	NSMC, New York
		Tumor glucose metabolism			
$[^{18}\text{F}]\text{FDG}$	2005	Alzheimer's disease (AD) and Frontotemporal dementia (FTD)			

NSMC, North Shore Medical Center, Manhasset, Long Island, NY; WMCCU, Weill Medical College of Cornell University, New York, NY.
 *The NDA holder ceased marketing this drug product in 1975. FDA currently lists sodium Fluoride F-18 injection in the Orange Book's "Discontinued Drug Product List."

1. Sr-82/Rb-82 generator 特性如下：

- (1) $[^{82}\text{Rb}]\text{RbCl}$ 是一種由 Sr-82/Rb-82 generator 之母核種 Sr-82 所湮滅產生的正子藥物，因 Rb-82 和鉀離子 (K^+) 生理活性很像，故可應用在心臟檢查。
- (2) 在注射 $[^{82}\text{Rb}]\text{RbCl}$ 後 0.5 分鐘，無論休息 (rest) 或承受壓力 (stress) 狀態下， $[^{82}\text{Rb}]\text{RbCl}$ 可快速由血液循環中清除。
- (3) 因 Rb-82 半衰期僅 75 sec，所以，使用劑量高達 30-60 mCi，且 10 分鐘內可獲得該需求劑量。
- (4) 因為可放出 β^+ 粒子的能量較高，所以得到相對差的影像品質。
- (5) Sr-82/Rb-82 generator 更換周期：28 天。
- (6) 商品化產品 CardioGen[®] 為一種自動化系統，可精確定量劑量。
- (7) 本檢查法所需時間：25 分鐘。

2. 理想狀態之心肌灌注掃描檢查，無論 rest 或 stress 狀態下，心肌對放射性示蹤物的吸收應與心肌血流 (Myocardial Blood Flow; MBF) 成正比，實際上，大多的心肌灌注檢查之核醫藥物吸收與 MBF 呈拋物線關係，以下圖來說， $\text{H}_2^{18}\text{O} > ^{18}\text{F}\text{-Flurpiridaz} > ^{99\text{m}}\text{Tc-Teboroxime} > [^{13}\text{N}]\text{NH}_4^+ > [^{82}\text{Rb}]\text{RbCl} > [^{201}\text{Tl}]\text{TlCl} > ^{99\text{m}}\text{Tc-MIBI}, ^{18}\text{F-FBnTP} > ^{99\text{m}}\text{Tc-Tetrofosumin}$ 。 H_2^{18}O 與 MBF 呈現趨近線性關係，而 $^{99\text{m}}\text{Tc-Tetrofosumin}$ 最差。



3. [⁸²Rb]RbCl、²⁰¹Tl]TlCl 與 MIBI 等三種核醫藥物進行全套 (full rest-stress) 心肌灌注掃描檢查之價格比較，如下表。

Tracer	Cost/pt
⁸² Rb]RbCl	210 EUR (for 100 p'ts) 140 EUR (for 150 p'ts)
²⁰¹ Tl]TlCl	120-180 EUR
MIBI	66 EUR (for one pt)+(costs of Tc-99m)

4. 結語：目前在歐洲地區，對於使用 [⁸²Rb]RbCl 正子藥物於 ischemic heart disease 診斷應用，有支持與反對二派理論，各自所述論點不同。支持者論點：製備簡易、美國地區具有長期使用經驗值、本法具有高精密度、準確性與專一性、全套檢查程序僅需 25 分鐘。反對者論點： [⁸²Rb]RbCl 正子藥物尚未取的歐洲藥品許可證、價格昂貴、僅可反應立即性的藥動特性、定量困難。

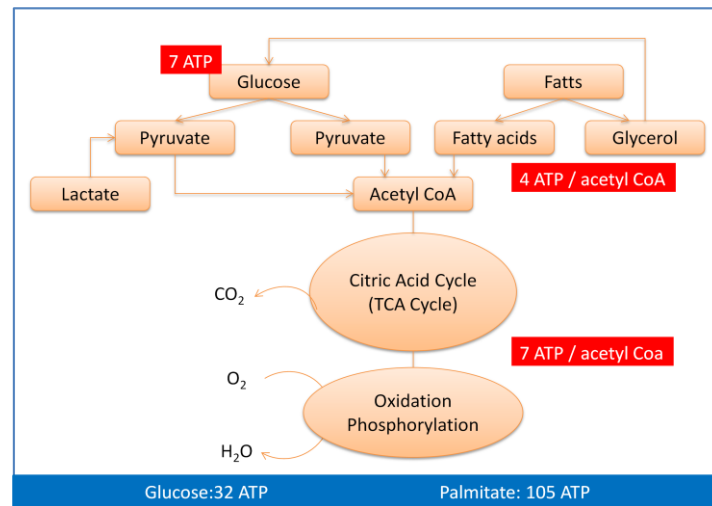
本國目前核醫界採行 ²⁰¹Tl]TlCl 或 ^{99m}Tc-MIBI 作為 ischemic heart disease 診斷工具。目前， [⁸²Rb]RbCl 也未具有 TFDA 核發之藥品許可證。若以與 MBF 線性關係來說， ²⁰¹Tl]TlCl 十分趨近 [⁸²Rb]RbCl，所以，大多醫院仍採用 ²⁰¹Tl]TlCl 進行檢驗。

(五) 核醫藥物如何評估心臟代謝功能

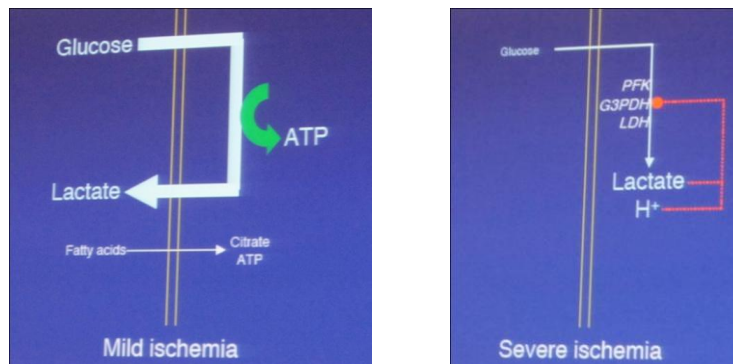
以核醫藥物對心臟代謝 (cardiac metabolism) 進行評估，先必須建立心肌之基礎生物化學概念。

- (1) 心臟是由高度能量需求之收縮肌肉所組成。
- (2) 心肌細胞富含粒線體 (mitochondria)，進行便利性有氧呼吸。
- (3) 只在有氧狀態下，心臟肌肉才具有功能。
- (4) 所有能量來源 (例如脂肪酸、葡萄糖或酮體) 均可被接受而代謝
- (5) 心肌無法儲存肝醣，所以無法作為能量儲存場所。

心肌正常情形下，其能量獲得多半依賴脂肪酸氧化作用 (fatty acid oxydation) 而得，但是，若心肌發生缺血情形時，脂肪酸氧化作用下降，而無氧醣解作用 (Anaerobe glycolysis) 則增加。下圖為正常情形下，心肌代謝不同分子所產生的 ATP 能量，由圖可知，一個葡萄糖分子可產生 32 ATP，而棕櫚酸則可產生 105 ATP。所以，雖所有能量來源 (例如脂肪酸、葡萄糖或酮體) 均可被接受而代謝，但主以脂肪酸為主。



如下圖可知，輕度缺血性心臟病(mild ischemia)與重度缺血性心臟病(severe ischemia)，體內代謝機轉與能量來源。



目前應用在心臟代謝研究的核醫藥物，包括^[18F]FDG、^[11C]-acetate 與^[11C]-Palmitate。

- (1) ^[18F]FDG：病患可以飲食且具有 glucose-insulin clamp，此 clamp 可刺激 glucose carrier (GLUT-4)的吸收，通常腫瘤研究上，一般處於飢餓狀態，此時具有高度脂肪酸代謝，反而沒有 FDG 吸收，例如糖尿病病患具胰島素阻抗作用，證明不會吸收葡萄糖。
- (2) ^[11C]-Palmitate 與 I-123-BMIPP(beta-Methyl-Iodo-Phenyl- Pentadecanoic Acid)：照影原理主要是利用心臟在缺血狀況下，脂肪酸代謝會受到抑制。
- (3) ^[11C]-acetate：屬於 one-stop shop 核醫藥物，free acetate 具有 65-70%穿透性，可以自血液循環進入細胞內代謝成 acetyl CoA，此特性可作為心肌灌注定量評估研究，且 washout 時間相當快約 2-3 分鐘左右，由於 washout 速度與氧氣消耗呈現性關係，故亦能作為氧氣代謝評估研究。

結語：仍以^[18F]FDG 為心臟代謝研究的核醫藥物。

(六) 個人化之分子影像藥物開發

演講者 Adrian D.Nunn 開宗明義以三方面探討個人化之分子影像藥物開發之必要性。為什麼要作? (Why?)、如何做? (How?) 以及做什麼? (What?)。

- Why?_(1)標靶治療藥物的確非常好，但是不同的個體，會有不同的反應。(2)Biomarkers 具有診斷與預後評估之價值。
- How?_(1)以法規面來審視具顯影效果的 biomarkers。(2)進行 in vitro 與 in vivo 結果比較。(3)根據結果篩選出新藥物進入臨床。(4)篩選出的新藥物取得藥品許可證。
- What?_(1)新藥物的研製必須符合未來需求。(2)例行生產供應新藥物。

以標靶治療核醫藥物為例，Herceptin 對乳癌治療效用佔 9%，但由於知道 Herceptin 具有心臟毒性（18%），目前僅被允許作為乳癌前導性治療藥物。Erbix 與 Avastin 分別對轉移性直腸癌治療效用佔 11-14%與 10%。換言之，標靶治療藥物施予在所有病患，其效用是不一致的。以目前非個人化設計的標靶藥物來說，除造成高花費、延遲治療效果外，甚至還有毒性存在。

臨床上有兩種生物標記（biomarker），一為診斷性標記（prognostic markers）：與臨床表徵有關，特別是與時間關聯的反應，例如：生存曲線。另一為預測性標記（predictive markers）：一般用來作為療效評估用途。癌症是屬於異質性（heterogeneity），而影像藥物可以提供部分區域（region）訊息，例如，Shah RB et al., 2004 進行攝護腺癌研究，指出具轉移性 HRPC 的單一個體可能具有異質性外觀、免疫表現型與基因型。原發性乳癌亦可能由數個異質性基因及不同細胞所組成。所以，單單出現標的是不夠的，還必須搭配血清分析與活體切片分析，綜合所有數據來進行分子影像之確立，進而找出影像生物標記（biomarker）。

以法規面來說，ICH M3(R2) June 2009 非臨床試驗數據導入人體試驗相關規範「Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals」指出，首要是 microdosing。美國 FDA 定義 biomarker 為可以預測疾病出現以及評估治療效果。並將之分成兩種：(1) qualified imaging biomarker，是指已被證實具藥物安全性與藥效，但仍不屬於被核可的藥物。(2) validated imaging biomarker，乃指已可確實針對某一適應症，更進一步確保藥物安全性與藥效。也就是說，這類藥物已是可商品化藥物，例如：Zevalin®與 Bexxar®。歐盟對於 biomarker 規範與美國相似。

過去美國 FDA 核可 ¹⁸F-FDG 適應症為不正常葡萄糖代謝(abnormal glucose metabolism) 評估，但並未核發可作為療效評估之許可證。美國 FDA 已於 2009 提出對於 PET cGMP 規範「PET Drugs-Current Good Manufacturing Practice (CGMP)」，明訂 Dec.12,2011 PET CGMP 規範即將落實施行。早期 ¹⁸F-FDG 若以現行規範審核，恐怕難以通過核可。現今，全球知名製藥廠如 GE、Siemens、Lantheus、BSP 與 MIP 等公司對於腫瘤、心臟血管與神經學方面等三大領域所進行的臨床試驗（phase I,II,III），如表四。而對於此類分子影像藥物，其藥品許可證之核發，必須分成兩階段，第一階段針對「生理作用機轉」核發，例如：plaque、glycolysis 檢驗。第二階段則針對「疾病診斷與療效評估」核發，例如：Alzheimer's disease、response to treatment。

表四、GE、Siemens、Lantheus、BSP 與 MIP 等公司進行的臨床試驗（phase I,II,III）

Clinical Trial phase	GE			Siemens			Lantheus			BSP			MIP		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
PET	oncology	FACBC	RGD		Hy	HY RGD	FLT				BBN	FE			
	cardiovascular							HF	Per						
	Neurology			Alz	Alz					Ms	Alz				
SPECT	oncology		RGD										Tro	Azd	Ona
	cardiovascular			HF											Zem
	Neurology			DA											

[note: ¹⁸FACBC = Prostate, RGD = Integrin targeted, Alz = Alzheimer's, HF = Heart failure, DA = dopamine Parkinson's, Hy = Hypoxia, FLT = DNA syn, Per = perfusion, BBN = ¹⁸Fbombesin, FE = ¹⁸F Glutamate, MS = PBR inflammation, Ona = Onalta, Azd = Azdra, Trp = Trofex, Zem = Zemiva (BMIPP)]

結語：個人化分子影像藥物並不是指藥局調劑動作與或是可以離院使用的。而是真正可觀察病患在接受治療後的生理變化、個人化的醫療行為、具有不同的商業模式與極佳的 Drug-Patient 對應性。

（七）分子影像藥物：診斷性 PET 正子藥物研製

根據調查顯示，全球人類平均壽命已可達 67 歲，亞洲地區的台灣、日本等國家，平均壽命甚至可達 80 歲以上。未來醫療趨勢朝向個人化醫療發展，分子影像藥物的開發符合此潮流，應用於特定疾病或特定個人。分子影像藥物應用範疇，可在偵測癌症代謝、細胞增生、腫瘤缺氧、β-amyloid plaque 以及基因表現等。目前，各種放射性核種（如：¹¹C、¹⁸F、⁶⁸Ga 等）標幟的核醫藥物數量繁多，作為各種疾病診斷用途。以 USA 執行臨床試驗現況來說，共計有 1,287 PET 臨床試驗案， [¹⁸F]標幟藥物佔 267 案，而 [¹¹C]佔 79 案，其他 PET 放射性同位素則超過 72 案。

Isotope	Halflife	Number of Listed Compounds	Diagnostic Applications
¹¹ C	20.38 min	114	Cancers: glioblastoma, prostate, myeloma, etc. Disease: Alzheimer's, brain, epilepsy Neuro: addiction, pain, brain mapping
¹³ N	9.97 min	1	Myocardial perfusion, pulmonary ventilation
¹⁸ F	109 min	146	Cancers: lung, liver, bone, melanoma, etc. Disease: inflammation, Alzheimer's, Response: chemotherapeutic efficacy
⁶⁴ Cu	12.7 hours	58	Cancer: cervical, colon, melanoma, etc.
⁶⁸ Ga	1.13 hours	12	Cancer: breast cancer, neuroendocrine tumors
⁷⁶ Br	16.0 hours	3	DNA Studies, antigens, nerves of the heart
⁸⁶ Y	14.7 hours	3	Lung cancer, melanoma
⁸⁹ Zr	3.27 days	5	Brain tumors, head and neck cancer
¹²⁴ I	4.18 days	12	Apoptosis, glioma, thyroid cancer, etc.

新型 PET 正子藥物合成有 microfluidic、In-capillary、Microwave、Single-Dose Microchemical 等四種方式，相較於傳統方式，縮短合成時間與提高產率。分述如下。

微流體 (microfluidic)。優點(1)反應體積十分小，易於控制。(2)增強系統內 mass 與 heat 傳遞，產生快速的反應動力，此種特質適合於短半衰期核種。(3)具有較佳產品特異性。(4)可降低試劑的耗損。(5)極小空間需求，屏蔽易於設計與阻隔放射線。目前 UCLA、Advion 與 TRASIS 公司所設計開發出的微流體設備，如圖。



毛細管 (In-Capillary)：反應試劑進入 Heated capillary 中，可增加放射化學純度與降低合成時間與花費，例如：利用 in-capillary 系統來合成 ^{18}F -FDG 只需 7 分鐘，且可得 80-85%產率。優點：可提供小型合成系統，免受狹小鉛室空間限制。降低開發時間。降低設備與材料預算。



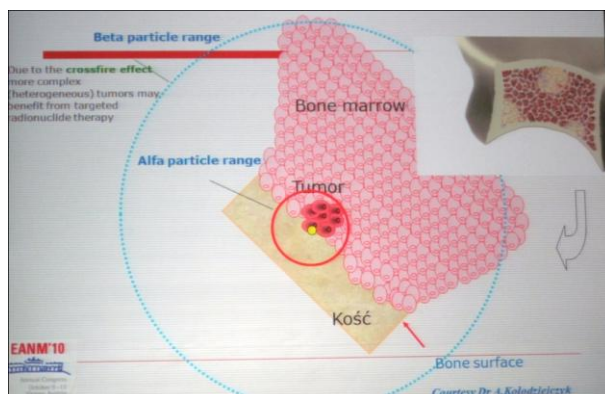
微波器 (Microwave)。優點：(1)可使混合溶液快速加熱，例如氟化反應。(2)易於加大反應體積，從 0.1mL 到 100mL。(3)藉由控制反應升溫與降溫週期，可增強勝肽合成與二級標幟反應。但必須考量儀器大小以及屏蔽設計。應用實例，Lu & Pike 應用 microwave 進行 ^{18}F -FDG 合成，可以得到 70%產率與 85%放射化學純度。(Lu & Pike, J.Nucl.Med. Meeting Abstracts. 2008, and Curr. Radiopharm. 2. 49-55, 2009)

單一劑量微量化學反應器 (Single-Dose Microchemical ; biomarker Generator)。設計特點：(1)10-15 mCi 單一劑量、每 30 分鐘即可進行一個反應週期，(2)可拋棄式化學合成組，(3)特殊控制卡，可針對 ^{18}F -FDG、 ^{18}F -FLT、 ^{18}F -NaF、 ^{18}F -FMISO 等不同核醫藥物合成控制，(4)尋求其他同位素應用可能性，(5)整合品管分析設備，(6)低放射線活度以及安全性之屏蔽設計考量。

(八) 分子影像藥物：標靶治療核醫藥物研製

分子影像核醫藥物可以觀察細胞與分子層次之活體組織生物反應過程、藉由極微量濃度 (10^{-6} - 10^{-12} mole/L) 分子影像藥物來觀察接受體與基因表現。用於治療用途之放射性核種生產方式有三種：(一)核子反應器 (Nuclear Reactors)：如 ^{131}I 、 ^{153}Sm 、 ^{166}Ho 、 ^{177}Lu 、 ^{47}Sc 等。(二)加速器 (Cyclotrons)：如 ^{47}Sc 、 ^{64}Cu 、 ^{89}Zr 、 ^{111}In 、 ^{211}At 。(三)發生器 (Generators)： $^{188}\text{W}/^{188}\text{Re}$ 、 $^{90}\text{Sr}/^{90}\text{Y}$ 、 $^{225}\text{Ac}/^{213}\text{Bi}$ 、 $^{227}\text{Ac}/^{223}\text{Ra}$ ，均必須以高比活度或是 non-carrier added 型式存在。但有其限制。例如：核子反應器產製的放射性核種，可能帶有高濃度的“cold” metal，另外，發生器產製的放射性核種，其化學分離過程可能導致污染發生。

治療原理主要基於放射性核種放出鄂惹電子(Auger radiation)、 α radiation emitters 與 β^- radiation emitters，破壞中程距離之癌細胞 DNA 以達癌症治療效果。以骨骼切面圖為例，即可知放射性核種發射 α emitters 與 β^- emitters 相對距離。



標靶治療核醫藥物設計，以放射性核種考量，其核種發射方式、半衰期 (half-life : 1-10days)、能量、low r-emission (dosimetry)、高比活度 (high specific activity)、標幟化學 (Labelling chemistry) 等方面。舉例來說，常見放射性核種特性，如下。

	Commercially radiocolloids			Bone pain palliation	
radionuclide	^{169}Er	^{186}Re	^{90}Y	^{89}Sr	^{153}Sm
Half-life	9.5	3.7	2.7	~50	1.9
emission	β	β, γ	β	β	β, γ

以半衰期來說，必須考量(1) in vivo residence time：放射性核種之物理半衰期必須能囊括從核醫藥物到達標的位置以及從身體清除之時間。(2) long-half life：半衰期必須足夠長，以避免核醫藥物到達標的位置前活度就顯著衰退。

以 Labelling chemistry 特性來說，必須探討影響核種與 ligand 反應動力學，包括溫度、時間、pH 等因子 (Breeman WAP et al., 2003, D.Pawlak et al., 2007, S.Jurrison et al., 2008)。例如，治療性核醫藥物 $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE 研究，Fe, Cu, Cd, Zn 金屬離子不純物的存在，造成 $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE 標幟產率的降低。其中，Fe 與 Lu,Y 有強烈的競爭性，當[Fe]小於 0.1umole/Ci ^{90}Y 或小於 2 umole/Ci ^{177}Lu ，[Cu],[Cd],[Zn]小於 0.25umole/Ci ^{90}Y 或小於 4.5 umole/Ci ^{177}Lu ，其標幟產率可以得到 98%以上。(D.Pawlak et al., 2007)

最佳化治療性核醫藥物之要件，(1)放射性核種必須與 carrier agent 結合，可使藥物穩定停留在 in vivo 狀況，讓 radiation 停留在期望的位置。(2)金屬離子特質：在水溶性環境中，必須維持穩定的氧化狀態，且是水溶性的 coordination chemistry，生理 pH 條件下，具有相對快速的錯合動力狀態 (complexation kinetics)。(3)每一種放射性金屬離子具有特異性，包括 ligand 的選擇、複合物形成安定性。(4)比活度 (specific activity)。

以比活度來說，成功的胜肽-接受體 (peptide-receptor) 治療核醫藥物，需要具備高比活度。原因在於接受體親和性以及接受體數量多寡。當 ligand 劑量增加，同時增加標幟與未標幟藥物對接受體的競爭性，當然，造成接受體的吸收多餘未標幟藥物，會有藥理作用 (pharmacological effects)。

標幟 ^{177}Lu 與 ^{90}Y 放射性核種之潛在優點來說，如下。

	potential advantages
Octreotide needed	$^{177}\text{Lu} < ^{90}\text{Y}$
Longer β -range [cross-fire]	$^{177}\text{Lu} < ^{90}\text{Y}$
Shorter half-life, higher dose-rate	$^{177}\text{Lu} < ^{90}\text{Y}$
Gammas available	$^{177}\text{Lu} > ^{90}\text{Y}$
Shorter β -range [better radiation]	$^{177}\text{Lu} > ^{90}\text{Y}$
Shorter β -range [lower glomerular radiation]	$^{177}\text{Lu} > ^{90}\text{Y}$

目前進行腫瘤治療臨床試驗之胜肽類核醫藥物，包括 somatostatin、CCK-B、Gastrin、Gastric releasing peptide、Bombesin、Neurotension、Sustance P 與 exendin-4 等。

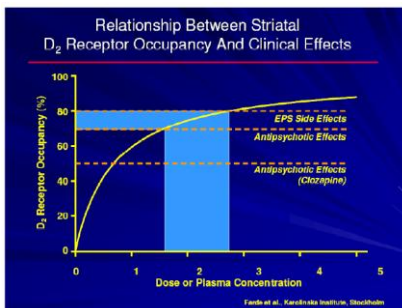
結語：以核醫藥物進行的分子放射療法，其發展潛能在於(1)標的組織之放射療法落實從實驗室到臨床 (from bench to bedside) 應用價值，(2)從巨觀到微小的疾病，可提供確實放射活度與化合物質量於疾病治療應用。(3)可與其他治療法 (例如：化療) 搭配使用。

(九) 從學術研究到產業應用之成功故事

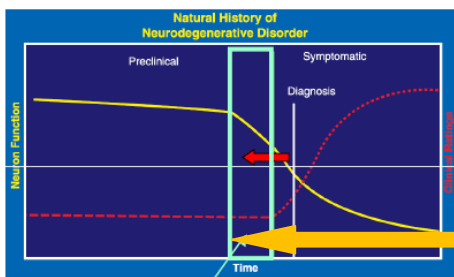
演講者為瑞典 Karolinska 機構 Christer Halldin 教授，闡述從學術研究到產業應用之成功故事，提及 PET 之所以成為「CNS 腦中樞神經系統藥物開發之熱門方法」，主因為 PET 具有下列特性：(1)Microdosing，(2)Drug occupancy at target of interest，(3)Biomarkers of pathophysiology。

(1) Microdosing: 開發 CNS 核醫藥物的關鍵因子在於 brain exposure，由藥物動力數據顯示，腦部過低 exposure 往往是照影失敗主要原因，而可藉由 PET-microdosing 來控制。Microdosing 指的是會產生藥理效應之 1/100 劑量與 < 100ug 藥物濃度。

(2) Drug occupancy at target of interest: 主要偵測 drug 結合 receptor 能力。可找出適當劑量，可以推估劑量或血漿濃度與 receptor occupancy 之間的關係，甚至於可作為 surrogate endpoint。例如：治療精神分裂症藥物 (antipsychotic drug) -Haloperidol 或 Clozapine。以血漿濃度或劑量變化當 x 軸與 receptor occupancy 當 y 軸作圖，以加入給予治療精神分裂症的效用以及錐體外徑的副作用 (extrapyramidal side effects, EPS) 作圖，來找出適當的劑量。

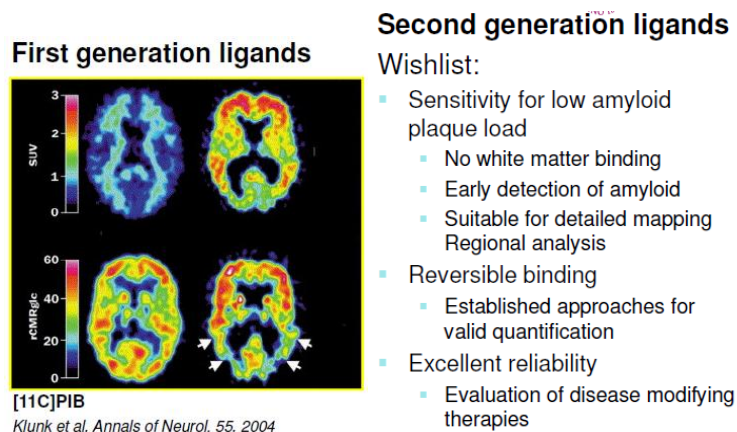


(3) Biomarkers of pathophysiology: 以早期神經退化疾病診斷來說，必須在明顯可被診斷的臨床徵兆出現前，即「無徵兆階段 Asymptomatic phase」，進行檢驗觀察。



Asymptomatic phase

Christer Halldin 教授針對 Alzheimer's disease 提出他的看法，因為第一代核醫藥物 ^{11}C PIB 會有白質區非特異性結合 (non-specific binding) (左下圖-箭頭處) 以及碳-11 半衰期僅有 20 分鐘。所以，與 AstraZeneca's 公司合作，進行第二代核醫藥物開發，例如 ^{11}C -AZD2184 與 ^{18}F -AZD4694 等。第二代藥物能具有(1)對 low amyloid plaque 具有敏感度：包括沒有白質區的結合等。(2)必須是可逆式結合反應。(3)具有高可靠性 (右下圖)。



(十) 拜耳先靈西藥部 (BSP) 發展願景

2006 開始，拜耳先靈西藥部 (Bayer Schering Pharma；簡稱 BSP) 朝向開發新正子核醫藥物，依序推出 F-18 Florbetaben、F-18 tumor metabolism、F-18 Prostate cancer、low radiation CT、F-18 Cardiac perfusion 等藥物，演講者 Thomas Dyrks 博士特別強調 PET tracer 是腦中樞神經之藥物開發主要工具，本次演講清楚描述如何進行腦中樞神經之新正子藥物評估週期。首先，先針對疾病專一性標的位置 (disease specific target) 設計出起始藥物 (new lead compound) 後，以第一步驟~第八步驟方式來評估。

第一步驟：Radiochemical purity and yield of new lead compound。

第二步驟：in vitro binding (radioactive competition assay)。

第三步驟：in vivo Biodistribution assay。

第四步驟：in vivo metabolism assay。

第五步驟：binding on postmortem tissue or animal model。

第六步驟：brain uptake in monkey。

第七步驟：preclinical and CMC development。

第八步驟：prepare for human PoM study。

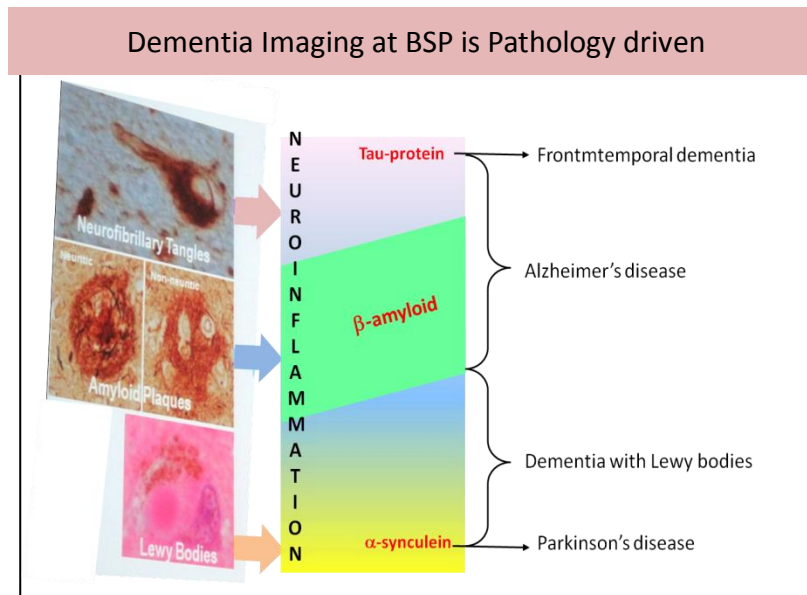
BSP 對於新正子藥物之發展策略：有效性之快速評估 (Rapid Evaluation of Efficacy)。先由搜尋國內外學術界研究計畫之研究成果，包括先期研究、臨床前數據、生化機轉之臨床數據佐證，來決定欲發展標的藥物。

目前，BSP 於影像醫學研究主要專注在(1)腦中樞神經系統：失智症 (dementia imaging) 與神經發炎 (neuroinflammation)。(2)腫瘤醫學：腫瘤代謝 (tumor metabolism)、攝護腺

癌 (prostate cancer) 與 stratification。(3)心臟血管：心臟灌注掃描 (Cardiac Perfusion)、血栓 (thrombosis) 與血管動脈硬化 (arteriosclerosis) 等三方面。

第一類：腦中樞神經系統：失智症與神經發炎藥物研發。

BSP 對於失智症[PET]方面的研究：主來自於病理學變化所驅動 (如下圖)。當神經發炎時，會產生β-amyloid plaques、tau tangles 與α-synuclein 聚集。Braak (1997) 依據觀察阿茲海默氏症 (Alzheimer's disease; AD) post-mortem 組織病理學上變化，將 AD 變化分為 A、B 與 C 三階段。到目前為止，對於 AD 診斷除了 post-mortem 的病理學變化外，尚可依據病變組織出現β-amyloid plaques 與 tau tangles 兩種特徵。



β-amyloid plaques 研究：墨爾本大學 Prof. Rowe 進行人體試驗，以 F-18 Florbetaben 注射健康個體(n=8)與 AD p't(n=10)，影像數據顯示，AD p't 新生皮層吸收值遠高於健康個體，且單就 AD p't 來說，小腦吸收值高且 washout 相當快，而大腦皮層吸收值略低，且 washout 相當緩慢。F-18 Florbetaben 可作為早期診斷 AD 之準確藥物，已在 2008 之 phase II 臨床研究得到證實 (THE LANCET (Neurology),vol 7, issue 2, 2008, p114-115)，目前正進行 phase III 臨床試驗中。本次年會探討有關 F-18 Florbetaben 的 topics，例如：OP219: Kinetic Modeling Of The β-Amyloid Tracer Florbetaben In Human Brains Using One And Two Input Functions。 OP220: New analysis tool for automated regional and voxelwise quantification of β-amyloid (Aβ) brain load as imaged by Florbetaben PET。 OP221: Phase 1 trials on Florbetaben β-amyloid brain PET in elderly normal controls - Influence of ethnic group, age, gender, and tracer mass dose。 OP354: Results of a multicentre Phase 2 trial to test Florbetaben for β-amyloid brain PET in Alzheimer's disease]。其中，OP221 與 OP354 獲得大會選拔為 highlight lectures。

此外，另一個藥物 Tg 2576，in vivo 實驗數據顯示結合於β-amyloid plaques，且白質 (white matter) 背景區的吸收值極低。目前同樣執行人體試驗以證明作用機轉。

Tau tangles 研究：Thomas Dyrks 博士指出，認為 AD 病程研究以 Tau tangles 為最佳方式，原因有三：(i) AD p't 很早就會出現 Tau tangles 聚集。(ii)與臨床徵兆的相關性較 Aβ佳。(iii) Tau tangles 是罹患 AD 之第二種病理特徵。所以，BSP 策略是開發 monitor Tau tangles 藥物，其適應症在於 AD 病程監測與確認 Tau tangles 之有無。

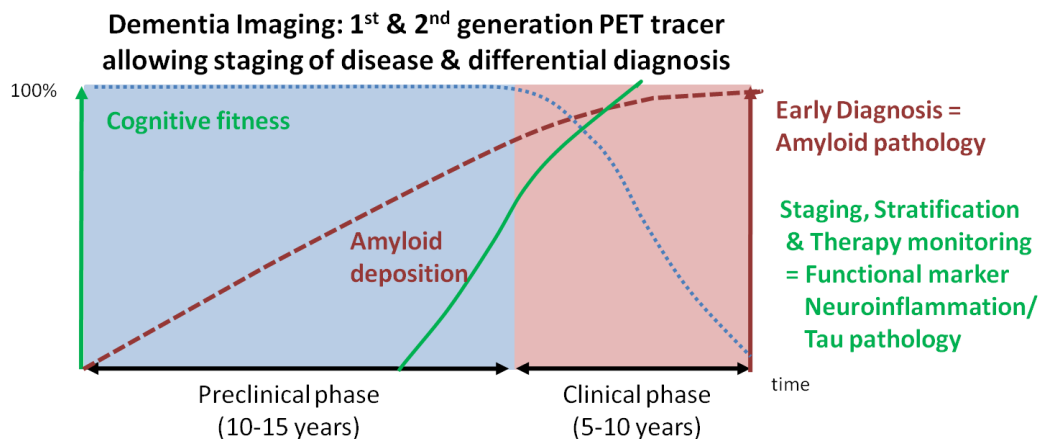
α -synuclein 研究：具有不同的診斷價值，通常 α -synuclein 聚集出現帕金森氏症（Parkinson's disease；PD）與路易氏體失智症（Lewy Body Dementia；DLB）病患。所以，BSP 策略是開發 monitor α -synuclein 藥物，其適應症在於區分 AD 與 DLB，早期診斷 PD 之有無。

BSP 對於神經發炎方面[PET]的研究，神經發炎現象是神經退化病程(neurodegenerative processes)之主要表徵，發炎程度受已活化腦部免疫細胞(microglia)與星狀細胞(astrocytes)來調控。

microglia 研究：microglia 可調節周邊苯二氮接受體（peripheral benzodiazepine receptor；PBR）表現，PBR 是一種轉運蛋白（Translocator protein；簡稱 TSPO）（18 kDa 分子量），為線粒體膜外蛋白質，存在於肝臟、心臟、腎上腺、睪丸、造血系統淋巴細胞以及大腦。透過 C-11 PK11195 臨床試驗，已經證明與 AD 有關聯，但可惜的是，F-18 PK11195 並未成功。目前另一藥物 F-18 PBR 正進行人體臨床試驗。[OP301: Biodistribution and radiation dosimetry of the peripheral benzodiazepine receptor (PBR) radioligand ^{18}F FEDAA1106: a human whole-body PET study]。

Astrocyte 研究：MAO-B 存在於星狀細胞中，是一種蛋白質，可選擇性氧化單胺類化合物，例如 o-tyramine 與 phenethylamine，可作為為神經退化/星形膠質細胞增生（astrocytosis）的 marker。F-18 DEP 3 與 C-11 Deprenyl 均顯示相似的結果，高達~7%的 brain uptake。[OP051: A Fluorine-18 Labelled Deprenyl PET Radioligand for in vivo Evaluation of MAO-B]。

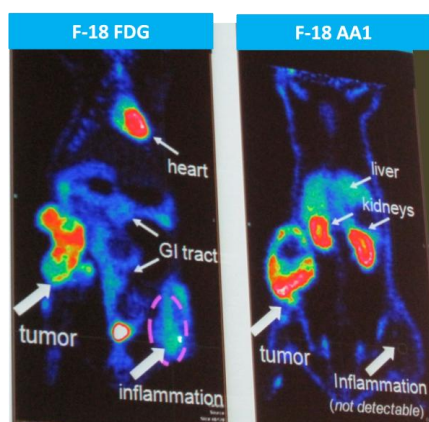
總而言之，對於失智症[PET]診斷核醫藥物的開發，第一代藥物主要在於早期 amyloid 病理變化診斷，而第二代藥物主側重在神經發炎病程分級、Tau 病理變化與治療監控等功能性 marker 的開發。腦中樞神經藥物研發仍是目前重點之一。



第二類、腫瘤醫學：腫瘤代謝、攝護腺癌藥物研發。

目前來說，F-18 FDG 在 oncology 臨床應用仍扮演極重之角色，但因為 FDG 屬於 non-specificity binding，例如，Schulthess 於 2006 以 PET/CT 進行肺癌研究影像，發現不容易與由放射治療所引發的發炎現象區分。所以，BSP 的目標是追求除了 FDG 以外的腫瘤造影藥物，策略有三：(1) Targeting Tumor Specific Metabolism：可明顯區分腫瘤與發炎位置、腦部代謝之影像改良。(2) Targeting Prostate cancer：利用 biopsy 清楚定位疾病的位置、利用核醫藥物釐訂病程以及可區分良性攝護腺增殖與癌症。(3) Early response assessment。

目前研究腫瘤代謝仍以 FDG 當成標準方法，但 BSP 開發 F-18 AA1 核醫藥物，利用 NCI-H460 rat 同時進行 F-18 FDG 與 F-18 AA1 實驗，結果發現 F-18 AA1 具有下列優點：(1) 藉由降低背景值，而提高訊號/雜訊比。(2) 明顯腫瘤與發炎的不同。(3) 對於生長緩慢的腫瘤（例如：攝護腺癌），提高照影影像品質。



同樣地，利用 NCI-H460 NSCLC rats 與 Turpentine inflammation rats 以 F-18 FDG 與 F-18 AA1 進行比較實驗，由左圖結果可知，發炎位置 FDG 顯示有高吸收影像，而 AA1 無顯著吸收現象。

其他，利用 F-18 Glu 衍生物(BAY85-8050)和 F-18 FDG 對肺癌病患進行代謝機轉研究比較，發現注射 BAY85-8050 (p.i 5-10 分鐘) 所得到影像與注射 F-18 FDG (p.i 60 分鐘) 之影像相同，也就是說，較早到擷取影像。此外，腦部背景值極低。

關於放射治療劑量反應評估，舉例說明，利用 F-18 FDG 與 C-11 MET、F-18 FLT、F-18 FMT 等數個 new tracers 偵測在 0,2,6,20,60Gy 不同放射治療劑量反應與 1,3,7days 不同天數之影像數據。接受放射治療後之影像結果發現：(1) FDG 部分：day1 與 day3，隨劑量增加，代謝十分活躍。(2) C-11 MET 與 F-18 FLT 部分：僅提供一部分有用的數據。(3) F-18 FMT 部分：顯示出最好的結果。

第三類、心臟血管：心臟灌注掃描 (Cardiac Perfusion)、血栓 (thrombosis) 與血管動脈硬化 (arteriosclerosis)

此部分並未多做著墨，但提及是具有發展潛力的。

結語：BSP 開發新正子核醫藥物聚焦在 CNS、oncology 與 Cardiovascular 等領域，目前，F-18 Florbetaben 已進入全球性臨床試驗 phase III 階段，當然，其他藥物研究正持續進行中。BSP 對內延聘生物、化學、藥學與影像各領域專業人才，對外積極與學校及其他藥廠合作，形成卓具強大研發能量之團隊，無庸置疑的，對於掌握正子藥物的開發契機來說，這絕對是致勝的關鍵點。

(十一) 核醫藥物與相關儀器之展示資訊

本次大會職利用大會、各座談會或訓練課程之間短暫的空檔，參觀核醫藥物與相關儀器展示並進行蒐集感興趣之產品資訊。參見附錄三。

1. $^{68}\text{Ge}/^{68}\text{Ga}$ generator 發生器 (IDB Holland bv company, www.idb-holland.com)

- (1) 具有 cGMP 級 $^{68}\text{Germanium}/^{68}\text{Gallium}$ generator ($^{68}\text{Ge}/^{68}\text{Ga}$ generator) 商品化產品。
- (2) ^{68}Ge 母核種產製： ^{68}Ge 母核種 (半衰期：270 days) 經由 $^{69}\text{Ga}(p,2n)^{68}\text{Ge}$ 反應產生的。
- (3) ^{68}Ga 子核種產製：以 5 mL 0.6N HCl 淘洗得到 ^{68}Ga (半衰期：68 min)， $\geq 80\%$ 產率。
- (4) ^{68}Ga 子核種應用：主要標幟於胜肽，作為腫瘤診斷與治療之正子藥物。
- (5) 產品類型：370MBq、740 MBq、1110MBq、1480MBq 與 1850MBq 等。

2. Draxmibi® 1 mg (IDB Holland bv company)

- (1) 適應症：心臟血流灌注掃描造影劑。
- (2) 產品特色：與 1-3 mL Tc-99m solution 調劑，Tc-99m 最大活度：11.1 GBq (300mCi) ，調劑後安定性可達 10 小時。與本所開發上市的 MIBI 產品，其相異點在於添加 Tetrafluoroborate (1 mg) 。

3. Lutetium-177 (¹⁷⁷Lu) trichloride Precusor 前驅物 (IDB Holland bv company)

- (1) 適應症：
- (2) 供應：全球性。
- (3) 規格：pH1.3、放射化學純度≥99%、於校正期之比活度為 37MBq-111GBq/mL，化學成分 LuCl3 in 0.05M HCl，¹⁷⁷Lu 物理半衰期 6.71 days，且放射 粒子特性。
- (4) 架儲溫度：15-20°C。
- (5) 產品體積：250uL、500uL、1 mL 等。

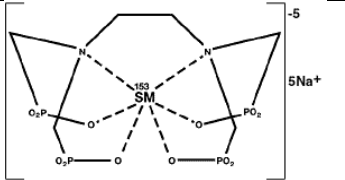
4. ^{99m}Tc-EC Injection (Institute of Isotopes Co. Ltd, www.izotop.hu)

- (1) 適應症：腎小管功能造影劑 (renal tubular functional imaging) 。
- (2) EC cold-kit 組成：共分成 A,B,C 瓶，各組成成分如下。

	Compositions
A vial	Ethylene-L,L-dicystein (API) Disodium hydrogenphosphatedihydrate Mannitol Ascorbic acid Sodium edatate
B vial	Stannous chloride dehydrate Tartaric acid Ascorbic acid
C vial	Potassium dihydrogenphosphate Ascorbic acid

5. ^{153m}Sm-EDTMP Injection (Institute of Isotopes Co. Ltd, www.izotop.hu)

- (1) 適應症：乳癌或攝護腺癌所導致骨轉移 (bone metastases) 之緩解止痛劑。
- (2) 調劑方式：由 A,B 瓶直接混合立即調劑 (On the spot) 而成。
- (3) 組成：共分成 A,B 瓶，各組成成分如下。

	Compositions	Structure
A vial	ethylenediaminetetramethylenephosphonic acid (EDTMP) (API) Stannous chloride dehydrate Ascorbic acid Glucose, anhydrous	

B vial	[¹⁵³ Sm] samarium chloride Sodium chloride Water for injection	
--------	--	--

6. NanoTek Microfluidic Synthesis System (Advion Co. Ltd, www.advion.com)

NanoTek Microfluidic Synthesis System 由 Advion 公司所開發，主要是針對正子核醫藥物建立快速、高效率合成平台。例如，同一時間內，¹⁸F 核種可與兩種不同的前驅物反應，產製兩種不同的正子核醫藥物。田納西大學 Akula, M.R., et al; and Collier T.L., et al 利用此系統同時產製 R&D 藥物 ¹⁸F-FLT 與 ¹⁸F-FMISO，目前，已可例行生產中規模批次量(200 mCi, 7.5 GBq)。

結語：核醫藥物與相關儀器發展相當快速，尤其正子核醫藥物。

(十二) 拜訪駐奧地利_台北經濟與文化代表處

本次除參與 23rd EANM 以及非正式拜訪駐奧地利_台北經濟與文化代表處 (Taipei economic and cultural office)。本次出國公差前，多次與本所派駐奧地利一級秘書洪煥仁博士接洽，溫文儒雅的洪博士相當熱心，提供許多的協助與幫忙，包括邀請函、簽證辦理、住宿安排、接送機與維也納當地情形概況介紹，對職來說，是一個相當珍貴的經驗與歷練，點點滴滴於心頭，感激之心實非筆墨可形容。



圖六、奧地利_台北經濟與文化代表處合影留念：(左圖:左至右排列) 經濟組陳韻如秘書、組長_林武智博士、職 修秀、文化組盧雲賓秘書。(右圖:左至右排列) 本所駐奧代表洪煥仁博士、組長_林武智博士、職 修秀、文化組盧雲賓秘書。

拜訪當日我們與代表處陳聯軍大使、文化組盧雲賓秘書與經濟組陳韻如秘書，討論有關本國核能發展方向及重要性、本國參與 IAEA 國際組織業務與關聯性、介紹本所開發核醫藥物之應用價值及目前對醫學診療之貢獻價值、再生能源之開發應用價值等，職 修秀從談話內容中，開闊國際視野與增廣相關見聞。

三、心得

本次公差從10月09日至10月13日，參加第23屆歐洲核醫學年會(23rdEANM)，參與各國專家場次之專題報告，並收集國際最新相關資訊，收穫相當豐富，心得敘述如下：

1. 這是職第一次參加歐洲核醫學年會，此行遇到台灣核醫學會理事長暨成大醫院核醫部主任_姚維仁醫師、台大醫院核醫部主治醫師_顏若芳醫師、台大醫院雲林分院核醫科主任_路景竹醫師、三軍總醫院核醫部主治醫師_黃文盛醫師、國防醫學院生物及解剖科研究所_馬國興副教授以及三軍總醫院核醫部[製藥組]_彭敬成主任與新光醫院主治醫師_沈業友醫師。十分感謝能有此機會結識核醫界頂尖翹楚之專科醫師暨研發人員朋友，也希望未來在於藥物開發之方向能與終端醫療體系臨床需求相結合，提供真正臨床迫切需求且極具診斷與治療關鍵價值之核醫藥物。
2. 因本所洪煥仁博士的協助與幫忙，幸運能拜訪奧地利_台北經濟與文化代表處，本次經驗彌足珍貴，了解本國核能發展方向及重要性、參與IAEA國際組織業務與關聯性、本所藥物開發方向等諸多內容，開闊國際視野與增廣相關見聞。
3. 新正子核醫藥物開發，最重要且關鍵的階段，是針對疾病專一性標的位置的藥物設計。目前，美國FDA提出eIND（2006），主要希望能先進行screening of candidate drugs，來真正選出標的藥物進入臨床階段。所以，職認為本組對於新正子核醫藥物開發，應從生物學觀點作為出發點，但最大挑戰在於疾病專一性標的位置的藥物設計思維與測試與candidate drugs選擇。
4. 本次年會討論有關腦神經藥物開發之相關議題，均以靈長類（primate）進行研究，這是本所隱憂所在。本所目前有關腦神經藥物開發之動物試驗之運作，大多以大鼠或小鼠進行，尚未提升至靈長類部分，對於此類藥物之開發較難與國際同步。
5. 本組多年來努力於開發診斷性核醫藥物，多項獲得本國食品藥物管理局（TFDA）藥物許可證，並且供應全國醫學中心及各級醫院臨床使用。且持續進行心臟血管、神經學科學以及腫瘤醫學等諸多人體臨床試驗，而本組目前也逐漸趨向治療性核醫藥物之開發。但無庸置疑的是分子影像藥物著實在基因體學與蛋白質體學研究，扮演舉足輕重的角色。

四、建議事項

本次參加第23屆歐洲核子醫學會研討會，除獲取核醫新知、知悉國際核醫研發現況外，更重要的是結識許多國內核醫界的專家朋友，依此次公差結果，對本所核醫藥物發展有如下建議。

- (一) 建立靈長類動物實驗中心：有助於將pre-clinical stage研發藥物提升到clinical stage人體試驗用藥水準，以佐證人體用藥之藥效與安全性評估。
- (二) 診斷性核醫藥物研製：進行腦中樞神經系統、腫瘤與心臟灌注掃描等PET正子新藥物研製，例如：F-18 Florbetaben。
- (三) 治療性核醫藥物研製：進行標靶治療核醫藥物之生理作用機轉研究探討。
- (四) 研製正子藥物快速合成設備：研製開發F-18快速合成系統、研製⁶⁸Ga/⁶⁸Ge合成系統。
- (五) 積極與著名學術單位合作：積極與國內外學者進行合作關係，不定期討論，尋求candidate新研發藥物。
- (六) 積極參與國際研討會：積極參與美國、歐盟與日本等先進國家舉辦之核醫藥物國際研討會及活動，尋求合作契機與確立研發方向。

五、附 錄

附錄一：發表於 23rd 歐洲核醫學年會_POSTERS 論文

1. An organic-resin generator for ⁶⁸Ga-PET labelling

Ming-Hsin Li, Jin-Jenn Lin, I-Lea Dai, Ther-Jen Ting, Wu-Jyh Lin

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taiwan.

Presentation Number: TP63

Session: TP3 - Technologist Poster Session 3

Objectives:

PET (positron emission tomography) is a powerful diagnostic and imaging technology which requires short-lived positron emitting isotopes. ⁶⁸Ga coupling to small bio-molecule is potentially an alternative to ¹⁸F- and ¹¹C-based radiopharmaceuticals. In particular, ⁶⁸Ga-peptides coupled receptors on tumor cells have shown pre-clinically and clinically high and specific tumor uptake. The ⁶⁸Ga deserves special attention because of its availability from long-lived ⁶⁸Ge/⁶⁸Ga generator systems which render ⁶⁸Ga radiopharmaceutical labeling independent of an onsite cyclotron.

Methods:

A novel type of a binary enriched-⁶⁹Ga/Ag alloy electrodeposited on silver substrate as a solid target was developed. It was successfully used for the preparation of ⁶⁸Ge/⁶⁸Ga generator. The deposition was carried out in an alkali solution containing gallium, silver and certain electrolytes at controlled current and ambient temperature that the quality of the deposits was proved to be suited for target irradiation. The operational specification of ⁶⁸Ge was 200 micro-Amperes at 26MeV proton bombardment for 12000 micro-Ampere-Hour on this deposits via the ⁶⁹Ga(p,2n) reaction. In the chemical process, a macroporous styrene-divinylbenzene copolymer was selected as an adsorbent for 10 mCi ⁶⁸Ge/⁶⁸Ga-generator and eluted by 0.1M sodium citrate.

Results:

However, the eluate is citrate form and normally contaminated with long-lived ⁶⁸Ge and other small amounts of Zn(II), Ti(II), Fe(III) and residuals. In a method, the citrate form conversion and its concentration and purification of the initial generator eluate are performed using an inorganic/organic column for ion exchanger.

Conclusions:

The retained radioactivity was eluted from the cartridge with 3mL of 0.1M HCl to yield a ⁶⁸Ga chloride solution free from citrate ion, ready to be used for labeling. It was revealed from long-term elution tests that approximately >95% of ⁶⁸Ga could be eluted from the generator column with 10 ml of 0.1M sodium citrate per elution, while the ⁶⁸Ge leakage was less than 0.0005% of the ⁶⁸Ge adsorbed on resin. The innovative generator exhibited a better performance in high radio- and chemical purities of the eluates are quite satisfactory for labeling applications.

[1] M.A. Green, J. Nucl. Med. 31 (1990) 1641.

[2] M.W. Greene, W.D. Tucker, Int. J. Appl. Radiat. Isot. 12(1961) 62.

[3] J. Yano, W.J. Skraba, H.H. Kramer, J. Nucl. Med. 5 (1964)484

2. An architectural innovation for PET Ga-68-DOTATOC radiopharmaceuticals automatic dispensing system

Ming-Hsin Li, Wu-Jyh Lin

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taoyuan, 32546, Taiwan.

Presentation Number: TP53

Session: TP3 - Technologist Poster Session 3

Objectives:

An automated PET radiopharmaceutical dispenser, that offers several advantages over manual procedures, has been developed. It employs a personal computer interfaced to a precision syringe drive module, a dose calibrator, and a printer. Traditional dispenser is not only inconvenient but also functionally limited. Without fast and continuous operation its dispensing cost is high. So filling process is difficult.

We illustrate an automated dispenser with a novel syringe for radiopharmaceuticals' filling, which has a completely automatic syringe filling process for dispensing PET radiopharmaceuticals (such as Ga-68-DOTATOC) in unit dose within syringe. Especially it refers to a situation in radiopharmacy that hand contact with radiopharmaceuticals is avoided and exposure to radioactive materials is reduced for operators.

Methods:

This architectural innovation include: a main unit with an activation mechanism to perform three-dimensional reciprocal movement and activate an injection needle to freely move in a predetermined space; a syringe rack located in the moving range of the injection needle by the main unit to accommodate a plural number of syringes, on each of which there is an injection hole; a drug bottle to keep high-dose radiopharmaceuticals; a drug pump with an inlet connecting to the drug bottle and an outlet connecting to the injection needle to withdraw the radiopharmaceuticals from the drug bottle to the injection needle and allow the front end of the injection needle activated by the main unit to go through an injection hole into the syringe and fill the PET radiopharmaceuticals into the syringe.

Results:

This innovative dispensing system can be carried out in hot cells where manipulation of syringes and vials by tongs and manipulators. It is also suitable for bench top applications, under laminar air flow cabinets or safety cabinets.

It can dispense PET radiopharmaceuticals like Ga-68-DOTATOC from a reservoir to aseptic syringes or dispense to aseptic vials in multiple aliquots, all with minimum manual handling. The total time to dispense a single dose from dispensing needle positioning in the syringe to removing the needle is typically 20 to 25 seconds. All the procedures meet the validation guidance of aseptic filling for injection.

Conclusions:

The automated radiopharmaceutical dispenser provides menu-selection operation and documentation of procedures and individual doses delivered. All materials in contact with the radiopharmaceutical are sterile and disposable. A novel transport safe is employed to further

reduce radiation exposure.

This syringe and dispensing system is specifically designed for high activity 511keV isotopes. The “PET radiopharmaceuticals automatic dispensing system” technology, developed and patented by INER(Institute of Nuclear Energy Research, Taiwan), makes the system fit dynamically on the specific needs of each PET radiopharmacy.

- Significantly reduces finger dose in bench-top dispensing situations
- Total cycle time of 20 – 25 seconds
- Increases accuracy, repeatability and throughput in dispensing operations
- Suitable for use with most types of syringes from 3mL up to 10mL size
- Vial shield accepts vials up to 10ml
- Stainless steel and plastic construction for easy cleaning and durability

References:

1. P.S. Plascjak, K. Kim, W. Meyer JR, etc., “An Automated Radiopharmaceutical Dispenser”, Appl. Radiat. Isot. 48, 345, 1997.
2. J.O. Park, Hyuk Lee, Y.S. Shin, etc., “Simple devices for dispensing [¹⁸F]FDG”, Appl. Radiat. Isot. 62, 605, 2005.
3. Adams, H.R., Channing, M.A., Divel, J.E., Dunn, B.B., Kiesewetter, D.O., Plascjak, P., Regdos, S.L., Simpson, N.R. and Eckelman, W.C., 1995. In: Emram, A.M., Editor, , 1995. Chemists' View of Imaging Centers, Plenum Press, New York, p. 175.
4. Capintec Inc., 1988. Radioisotope Calibrator Owner's Manual for Models CRC-7, CRC-12 and CRC-120. , Rev. F. Capintec Inc., Pittsburg, Pa.

3. Simple, fast preparation of gallium chloride from the Ga-67-citrate injection

Ming-Hsin Li, Wu-Jyh Lin, Jin-Jenn Lin, I-Lea Dai, Ther-Jen Ting

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taoyuan, 32546, Taiwan.

Presentation Number: TP23

Session: TP2 - Technologist Poster Session 2

Objectives:

We have developed a simple, highly efficient, and rapid technique for preparation of gallium-67 chloride from the Ga-67-citrate solution. The need for such a conversion relates to the formation of a strong complex between gallium ions and citrate preventing that the binding of Ga-67 to selected molecules in labeling procedures.

Methods:

Because of the Ga-67-citrate injection is a popular solution in radiopharmacy, we attempting to label DOTA-TATE or DOTATOC with Ga-67 prior to Ga-68 and likewise required substitution of the citrate ions for Cl (1 minus) prior to the radio-labeling procedure. We use a simple two-step procedure involving absorption on a silica-gel, removal of the citrate ions with water and elution of the Ga-67 ions with diluted HCl.

Results:

This rapid procedure characterizes a minimum amount of manipulation of the radioactivity and is high efficiency reproducible. The two steps:

1. The 5 mL of Ga-67(100 MGq, INER, Taiwan) was added 10 mL of distilled water, whereafter the solution was filtered over a 500mg silica-gel cartridge (Waters, USA) fitted with a 6-ml plastic syringe, at a flow rate of 1 mL per minute.
2. The retained radioactivity was eluted from the cartridge with 3 ml of 0.1 M HCl and the pH of the eluate was adjusted to pH 5 with 0.1 N NaOH to yield a Ga-67 chloride solution free from citrate ions.

Conclusions:

This simple procedure was completed in 20 min and the overall recovery of the radioactivity exceeded 90%. We are currently using silica-gel (SiOH) cartridges routinely in our laboratory for the preparation of Ga-67 chloride from the citrate solution for the radiolabeling of DOTA-TATE or DOTATOC.

References:

1. Chan H-K, Gonda I. A simple method for the preparation of gallium chloride from the citrate solution. *Eur J Nucl Med* 1991 ;18:860.
2. Green MA, Welch MJ. Gallium radiopharmaceutical chemistry. *Nucl Med Biol* 1989; 16 : 435-448.
3. Furukawa T, Fujibayashi Y, Fukunaga M, Yokoyama A. Gallium labeling of immunoglobulin G with high specific radioactivity. *Chem Pharm Bull (Tokyo)* 1990; 38:2285 2286.

4. Assessment of irradiation parameters for Ga-68/Ge-68 generator

Ming-Hsin Li, Ting-Shien Duh, Jin-Jenn Lin, Ther-Jen Ting, Wu-Jyh Lin

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taiwan.

Presentation Number: TP15

Session: TP1 - Technologist Poster Session 1

Objectives: This research is related to a process parameters assessment method for the solid target of Ga-68/Ge-68 generators. Especially, it refers to a parameter assessment method with easy prediction, control and consistent quality in radiation products.

Traditional irradiation for Ga-68/Ge-68 generator does not consider radiation energy dose and electroplating thickness of Ga-69, which result in both inaccurate dose prediction and many impurities formed (such as the Zn-65). Therefore, when the Ga-68 washed from the generator is used for drug labeling, the metal ions in impurities will interfere with pretreatment efficiency and lower drug labeling yield.

Methods:

- a. Calculate the thickness d for the electroplated Ga-69 on the solid target;
- b. On a graph of incident energy decay curves comprising a plural number of different irradiation energy doses X_i and target thickness, select a decay curve with a default irradiation energy dose X_i , and based on the electroplating thickness d derive the relative irradiation energy dose Y_i after decay;
- c. On a graph of corrected function curves for Ga-69(p,2n)Ge-68 incident energy and reaction cross-section with different Ge-68, Ga-68, Zn-65 irradiation doses and cross-sectional area, based on the defined position by irradiation energy dose X_i and the corresponding irradiation energy dose Y_i , derive the two nuclear reaction cross-sectional areas corresponding to Ge-68 and figure out the mean reaction area (MRA); by the same means, derive the two nuclear reaction cross-sectional areas corresponding to Ga-68 and the two nuclear reaction cross;
- d. Derive a plural number of groups of MRAs corresponding to Ge-68, Ga-68, Zn-65;
- e. Select the maximum MRA corresponding to Ge-68 and the minimum MRA corresponding to Ga-68 and Zn-65, and generate the required default radiation dose for each reaction cross-sectional area in the group, which is the optimal reaction energy.

Results:

The irradiation energy parameters derived from the above assessment are used in cyclotron irradiation to generate the best yield and the minimal other nuclides. The actual irradiation parameters are as follows:

1. Irradiation energy: 26 MeV
2. Accelerated particle: proton
3. Beam current: 200 micro-A
4. Irradiation time: 60 hrs

Conclusions: It can be known the aforementioned innovation for the Ga-68/Ge-68 generator proves to be predictive and controllable. Moreover, the irradiation products have consistent quality. Therefore, the present results have proved to possess industrial usefulness, novelty and progressiveness.

5. Comparative Therapeutic Efficacy of ¹⁸⁸Re-Liposomes and 5-FU in LS-174T human Colon Carcinoma Solid Tumor xenografts

Chin-Wei Hsu¹, Chih-Hsien Chang¹, Ya-Jen Chang¹, Te-Wei Lee¹ and Gann Ting¹

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taiwan.

Poster Number: PW02

Poster Session: Poster walking tour 2

Nanoliposomes are important carriers capable of packaging drugs for various delivery applications. Rhenium-188 (¹⁸⁸Re) radiolabeled liposomes (¹⁸⁸Re-Liposome) own the potential in radiotherapy and diagnostic imaging. The 5-fluorouracil (5-FU), the first choice of chemotherapy for treating colon cancer patients, has been reported to have considerable toxicity administered by intravenous injections or via alimentary treat. The purpose of this study was to investigate the maximum tolerated dose (MTD) of ¹⁸⁸Re-Liposome and 5-FU in normal nude mice by i.v. injection. The biodistribution of ¹⁸⁸Re-Liposome administered by the i.v. route in murine LS-174T human colon adenocarcinoma-bearing nude mice were investigated. MicroSPECT/CT images were performed to evaluate the distribution of drug in the tumor mouse model. Furthermore, comparison of therapeutic efficacy between ¹⁸⁸Re-Liposome and 5-FU in LS-174T colon adenocarcinoma mice was evaluated. According to the measurement of body weight and survival, the MTD of ¹⁸⁸Re-Liposome and 5-FU were 29.6 MBq and 180 mg/kg, respectively. For the biodistribution study, the highest uptake in LS-174T tumor was found to be 11.27% ± 0.99% at 24 h, and the tumor to muscle ratio of ¹⁸⁸Re-Liposome was 16.07% ± 1.91%. MicroSPECT/CT imaging indicated the highest uptake of ¹⁸⁸Re-liposome in LS-174T tumor in nude mice at 24 h after injection. The imaging analysis showed a positive correlation of tumor targeting of ¹⁸⁸Re-liposome between biodistribution and microSPECT/CT imaging. For therapeutic efficacy, the large tumor-bearing mice (~300 mm³) treated with radiotherapeutics of ¹⁸⁸Re-Liposome (4/5 MTD, 23.7 MBq) showed better tumor growth inhibition and longer survival time than those treated with chemotherapeutics of 5-FU (4/5 MTD, 144 mg/kg). The median survival time for mice treated with ¹⁸⁸Re-Liposome (53.78 days; P<.05) and 5-FU (43.17 days; P>.05) was better than those from normal saline treated mice (25.88 days). These results suggested the potential and advantage of ¹⁸⁸Re- liposomes for imaging and treatment of malignant diseases.

6. Evaluation of Acute Toxicity of ^{188}Re -BMEDA-liposome in Rats

Chi-Mou Liu^a, Chih-Hsien Chang^a, Ya-Jen Chang^a, Chin-Wei Hsu^a, Liang-Cheng Chen^a, Chung-Li Ho^a, Chia-Yu Yu^a, Tsui-Jung Chang^a, Tung-Chuan Chiang^a, Te-Wei Lee^a

Institute of Nuclear Energy Research, Isotope Application Division, Longtan, Taiwan.

Poster Number: 18

Poster Session: P14

Liposomes can selectively target cancer sites and carry payloads, thereby improving diagnostic and therapeutic effectiveness and reducing toxicity. To evaluate therapeutic strategies, it is essential to use animal models reflecting important safety aspects before clinical application. The objective of this study was to investigate acute radiotoxicity of ^{188}Re -N,N-bis(2-mercaptoethyl)-N',N'-diethylethylenediamine (BMEDA)-labeled pegylated liposomes (^{188}Re -BMEDA-liposome) in female Sprague-Dawley rats. Rats were administered with ^{188}Re -BMEDA-liposome, normal saline as blank or non-radioactive liposome as vesicle control via intravenous injection and observed for 14 days. Examinations have been conducted with respect to mortality, clinical signs, food consumption, body weights, hematological and biochemical analyses. In addition, gross necropsy, histopathological examinations and cytogenetic analyses were also performed at the end of the follow-up period. None of the rats died and no clinical sign was observed during the 14-day study period. Rats administered with ^{188}Re -BMEDA-liposome at dosage of 185 MBq displayed a significant weight loss compared with the control from study day (SD) 1 to SD 4, and the white blood cell count reduced to 5-10% of initial value (female: 18.55 ± 6.58 to $0.73 \pm 0.26 \times 10^3/\mu\text{L}$; male: 14.52 ± 5.12 to $1.43 \pm 0.54 \times 10^3/\mu\text{L}$) 7 days post injection, but found to recover on SD 15. There was no significant difference in biochemical parameters and histopathological assessments between the ^{188}Re -BMEDA-liposome-treated and control groups, the frequencies of dicentric chromosomes (DCs) were associated with dosage of ^{188}Re -BMEDA-liposome. The information generated from this study on acute toxicity will serve as a safety reference for further subacute toxicity study in rats and human clinical trials.

Keywords: acute toxicity, radiopharmaceutical, radiotoxicology, ^{188}Re -BMEDA-liposome, Sprague-Dawley rats.

附錄二：23rd EANM 歐洲核醫學年會_議程

6

Scientific Programme

ANNUAL CONGRESS OF THE EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

Outline Scientific Programme

Saturday, October 9, 2010

TIME SCHEDULE										
Time/Halls	D	E1	E2	F1	F2	G/H	I	K	P	U2D441
Cap.	1,400	500	500	500	500	440	220	220	100	90
08:00 - 17:00			Pre-Congress Symposium		EANM Task Group & Committee Meetings (16:00 - 18:00)	UEMS/EBNM Delegates Meeting (16:00 - 18:00)	Advisory Council Meeting (11:00 - 13:00) EANM Delegates Assembly (14:00 - 16:00)	ESNM Meeting (14:00 - 16:00)		
19:00 - 20:00	EANM '10 Opening Ceremony (Hall A) & Welcome Reception (20:00 - 22:30)									

	New Features (please see page 14)
	Industry Lunch Meetings
	CME
	Symposia/Pre-Congress Meetings
	Poster Walks
	Parallel Sessions
	Featured Parallel Sessions
	Plenary/Awards/Highlights
	Technologist Sessions

Outline Scientific Programme

Sunday, October 10, 2010

TIME SCHEDULE										
Time/Halls	D	L1	E2	F1	F2	G/H	I	K	P	U2D441
Cap.	1400	500	500	500	500	440	220	220	100	90
08:00 - 09:30	101 CME 1: Cardiovascular Practical aspects of PET imaging in patients with Ischaemic Heart Disease	102 Symposium 1	103 Poster Walks Poster Exhibition Hall (08:30 - 09:30)	104 Technologists (08:00 - 08:12) Opening Ceremony 08:15 - 09:45 CIE 1					06:30 - 07:00 Breakfast 07:00 - 08:00 Industry Meeting	110 08:00 - 09:30 Pitfalls & Artefacts (Interactive)
10:00 - 11:15	201 Plenary Session 1 Incl. Marie Curie Lecture: Highlights in molecular imaging: Present & future		203 Featured 1	204 In Hall D: Plenary Session 1 Incl. Marie Curie Lecture: Highlights in molecular imaging: Present & future						
11:30 - 13:30	301 CME 2: Physics Radiation exposure in NM and multi- modality imaging	302 Symposium 2	303 Featured 2	304 Technologists Oral Presentations 1	305 Parallel Session	306 Parallel Session	307 Parallel Session	308 Parallel Session	309 Parallel Session	
13:40 - 14:30	Industry Lunch Symposia				Industry Lunch Symposia					Daily Forum for „Young EANM“
14:30 - 16:00	401 CME 3: Drug Development & Radiopharmacy Personalizing radiopharmaceuticals	402 Symposium 3	403 Featured 3	404a Technologists 14:30 - 15:30 Mini Course 1 15:45 - 16:45 Mini Course 2 17:00 - 18:00 Mini Course 3	405 Parallel Session	406 Parallel Session	407 Parallel Session	408 Parallel Session	409 Parallel Session	
16:30 - 18:00	501 CME 4: Dosimetry Preclinical targeted radionuclide therapy	502 Symposium 4	503 Featured 4		505 Parallel Session	506 Parallel Session	507 Parallel Session	508 Parallel Session	509 Parallel Session	

OCTOBER 9 - 13, 2010 · AUSTRIA CENTER VIENNA · AUSTRIA

2010



Scientific Programme

Outline Scientific Programme

Monday, October 11, 2010

TIME SCHEDULE										
Time/Halls	D	E1	E2	F1	F2	G/H	I	K	P	U2D441
Cap.	1.400	500	500	500	500	440	220	220	100	90
08:00 - 09:30	801 CME 5: Paediatrics Renal scans and the rising of MRI	602 Symposium 5	803 Poster Walks Poster Exhibition Hall (08:30 - 09:30)	604 Technologists CTE 2					06:30 - 07:00 Breakfast 07:00 - 08:00 Industry Meeting	110 08:00 - 09:30 Pitfalls & Artefacts (Interactive)
10:00 - 11:15	701 Plenary Session 2: Do we need guide- lines in reporting?		703 Featured 5	704 In Hall D: Plenary Session 2: Do we need guide- lines in reporting?						
11:30 - 13:00	801 CME 6: Oncology How to design a clinical trial	802 Symposium 6	803 Featured 6	804 Technologists Oral Presentation 2	805 Parallel Session	806 Parallel Session	807 Parallel Session	808 Parallel Session	809 Parallel Session	
13:00 - 14:30	Industry Lunch Symposia			EANM Tech members General Meeting	Industry Lunch Symposia					Daily Forum for „Young EANM“
14:30 - 16:00	901 CME 7: Molecular Imaging & Drug Development & Radiopharmacy New radio- pharmaceutical developments in oncology	902 Symposium 7	903 Featured 7	904 Technologists CTE 3	905 Parallel Session	906 Parallel Session	907 Parallel Session	908 Parallel Session	909 Parallel Session	
16:30 - 18:00	1001 CME 8: Therapy Radionuclide therapies in liver cancer	1002 Symposium 8	1003 Featured 8	1004 Technologists CTE 4	1005 Parallel Session	1006 Parallel Session	1007 Parallel Session	1008 Parallel Session	1009 Parallel Session	

ANNUAL CONGRESS OF THE EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

Outline Scientific Programme

Tuesday, October 12, 2010

TIME SCHEDULE										
Time/Halls	D	E1	E2	F1	F2	G/H	I	K	P	U2D441
Cap.	1.400	500	500	500	500	440	220	220	100	90
08:00 - 09:30	1101 CME 9: Interactive - Cardiovascular Case readings gated SPECT, Case readings CT gated SPECT	1102 Symposium 9	1103 Poster Walks Poster Session Exhibition Hall (08:30 - 09:30)	1104 Technologists Poster Session 1,2,3					06:30 - 07:00 Breakfast 07:00 - 08:00 Industry Meeting	110 08:00 - 09:30 Pitfalls & Artefacts (Interactive)
10:00 - 11:15	1201 Plenary Session 3: Integrating imaging centers of excellence		1203 Featured 9	1204 In Hall D: Plenary Session 3: Integrating imaging centers of excellence						
11:30 - 13:00	1301 CME 10: Interactive - ESNM Faculty Bone: Technetium, F-18, Non-oncological	1302 Symposium 10	1303 Featured 10	1304 Technologists	1305 Parallel Session	1306 Parallel Session	1307 Parallel Session	1308 Parallel Session	1309 Parallel Session	
13:00 - 14:30	Industry Lunch Symposia				Industry Lunch Symposia					Daily Forum for „Young EANM“
14:30 - 16:00	1401 CME 11: Interactive - PET/ CT Revision Group Hybrid Imaging in oncology	1402 Symposium 11	1403 Featured 11	1404 Technologists CTE 5	1405 Parallel Session	1406 Parallel Session	1407 Parallel Session	1408 Parallel Session	1409 Parallel Session	
16:30 - 18:00	EANM Members Assembly			CTE Examination						

OCTOBER 9 - 13, 2010 · AUSTRIA CENTER VIENNA · AUSTRIA

Scientific Programme



Outline Scientific Programme

Wednesday, October 13, 2010

TIME SCHEDULE										
Time/Halls	D	E1	E2	F1	F2	G/H	I	K	P	U2D441
Cap.	1,400	500	500	500	500	440	220	220	100	90
08:00 - 08:30	1601 CME 12: Neuroimaging Role of Nuclear Medicine in depression and associated illness	1602 Symposium 12	1603 Featured 12	1604 08:30 - 10:45 CTE 6	1605 Parallel Session	1606 Parallel Session	1607 Parallel Session	1608 Parallel Session	1609 Parallel Session	
10:00 - 11:30	1701 CME 13: Radiopharmacy & Radionuclide Therapy Antibody based radiopharma- ceuticals	1702 Symposium 13	1703 Featured 13	1704 Technologists 10:45 - 11:15 Closing Ceremony	1705 Parallel Session	1706 Parallel Session	1707 Parallel Session	1708 Parallel Session	1709 Parallel Session	
11:45 - 13:15	1801 11:45 - 12:00: Awards Ceremony 12:00 - 13:00: Highlights Lecture 13:00 - 13:15: Closing Ceremony			1804 In Hall D: 11:45 - 12:00: Awards Ceremony 12:00 - 13:00: Highlights Lecture 13:00 - 13:15: Closing Ceremony						

附錄三：23rd EANM 歐洲核醫學年會_攜回資料

攜回資料名稱及內容

- (1) Ge-68/Ga-68
- (2) Draxmibi[®] 1 mg
- (3) LuMark
- (4) Multibone, in vivo kit for 'on the spot' preparation of ¹⁵³Sm-EDTMP injection
- (5) Ethylene-L,L-dicystein (EC), in vivo kit for preparation of ^{99m}Tc-EC injection
- (6) Final Programme: Annual Congress of the European Association of Nuclear Medicine
- (7) Nuklearmedizin 2010; 49: 125-172