中华医学会核医学分会第十一届委员会
技术与继续教育学组

中国医学装备协会核医学专委会
2019年年会　特邀专家讲座

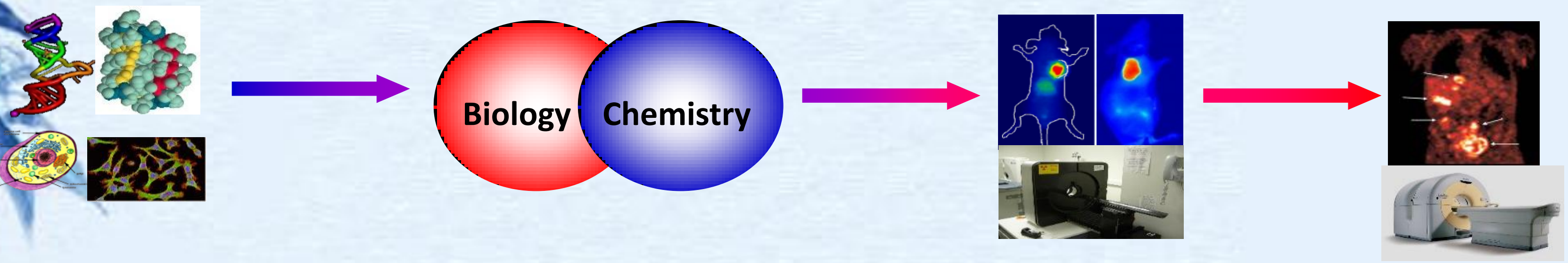
SPECT药物和设备的自主创新推动核医学分子影像发展

专家姓名 贾兵
专家单位 北京大学医学同位素研究中心

分子影像成为精准医学的重要内容

中华医学会核医学分会
技术与继续教育学组

In Vitro　　　　In Vivo

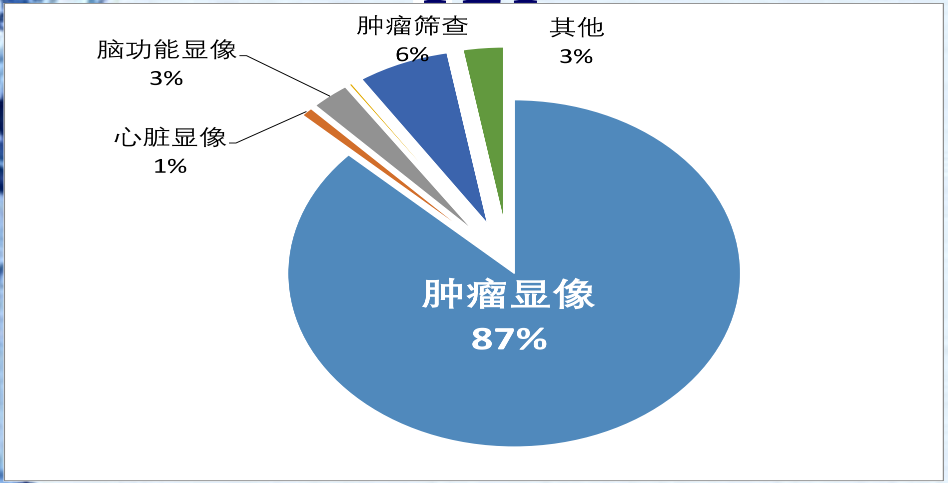


生物靶点筛选　　分子影像探针制备和优化　　小动物成像　　临床应用

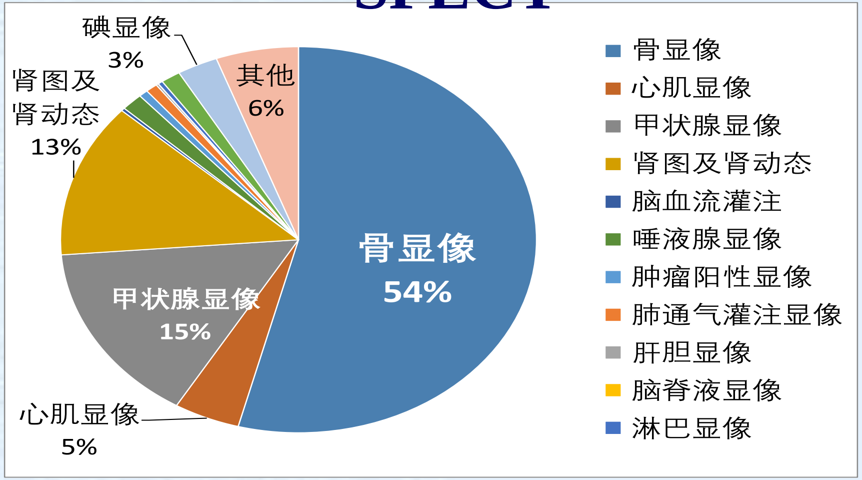
眼见为实

核医学显像临床应用

PET



SPECT



中国：~260万例/年

~800 SPECT

~400 PET

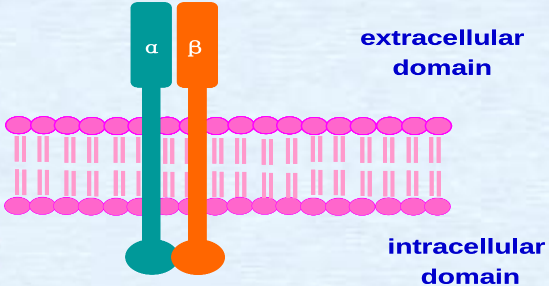
美国：~2000万例/年

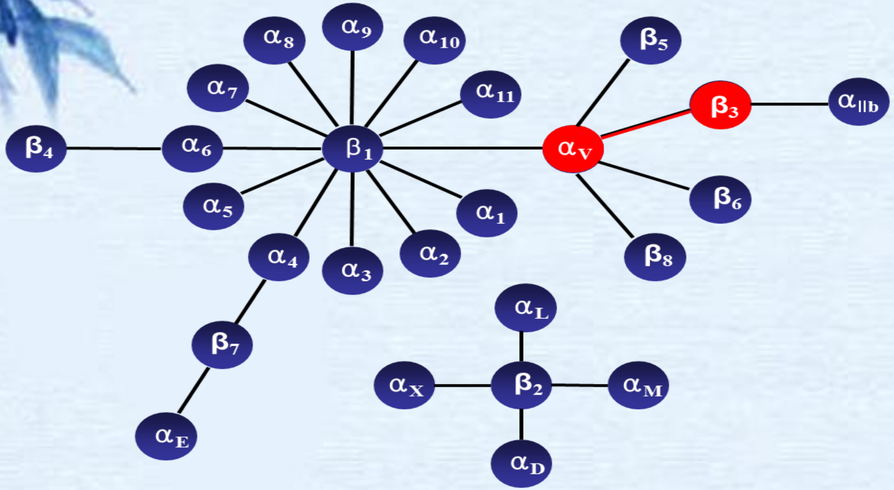
~15000 SPECT

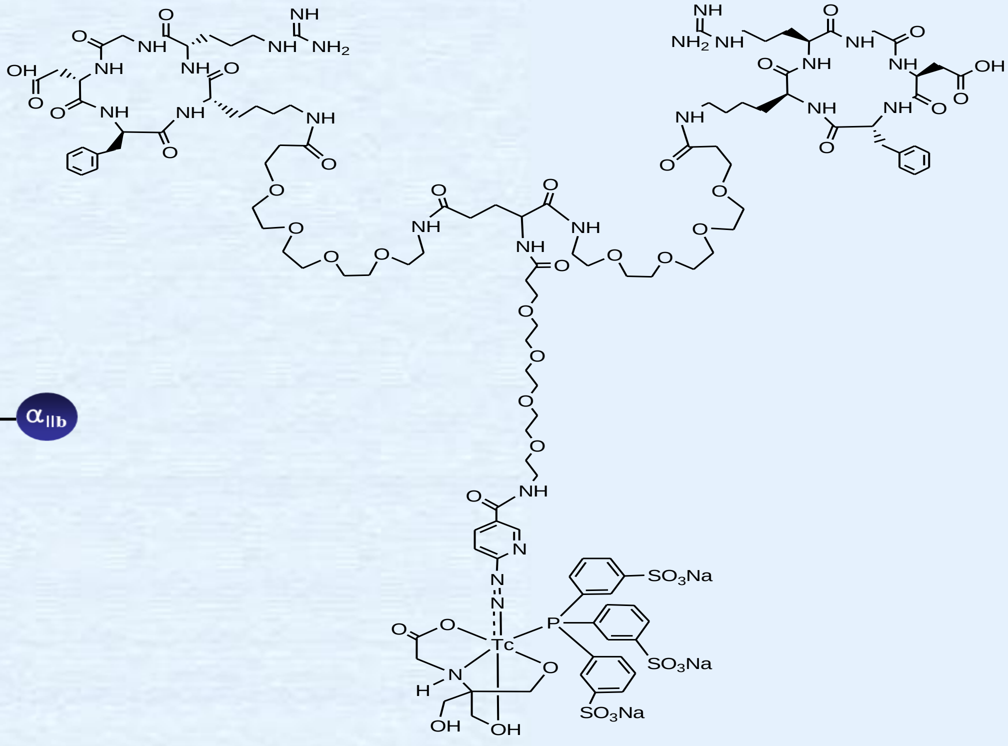
~2000 PET

新型RGD分子探针

Integrin heterodimer

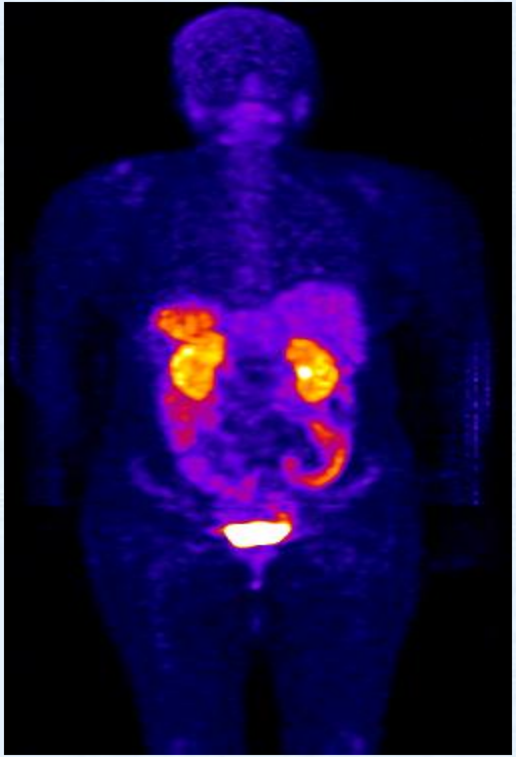




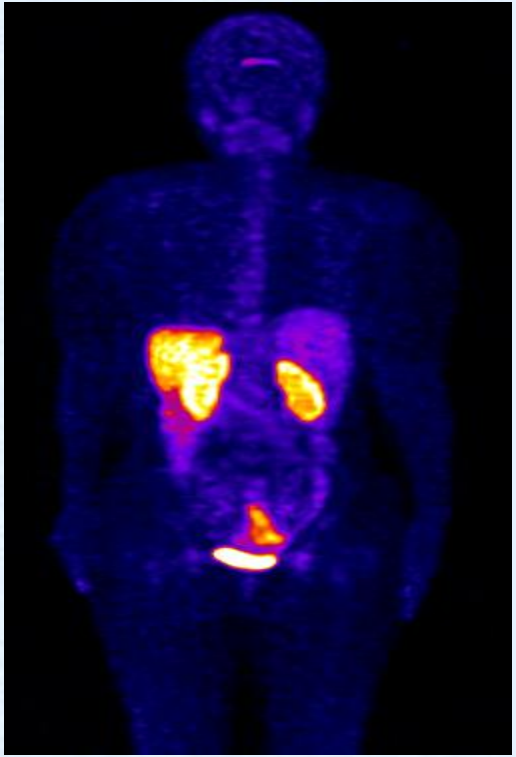


[^{99m}Tc(HYNIC-3P-RGD2)(tricine)(TPPTS)]: ^{99m}Tc-3PRGD2

^{99m}Tc-3PRGD2/SPECT图像



健康志愿者1



健康志愿者2

临床应用—肺癌患者

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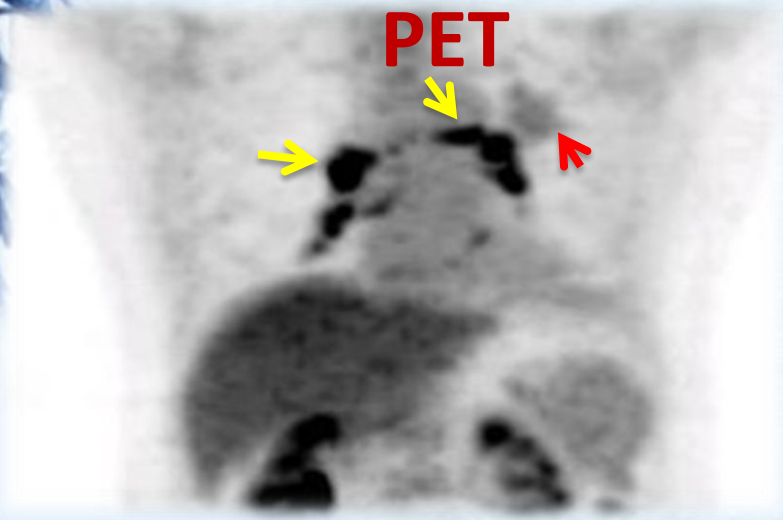
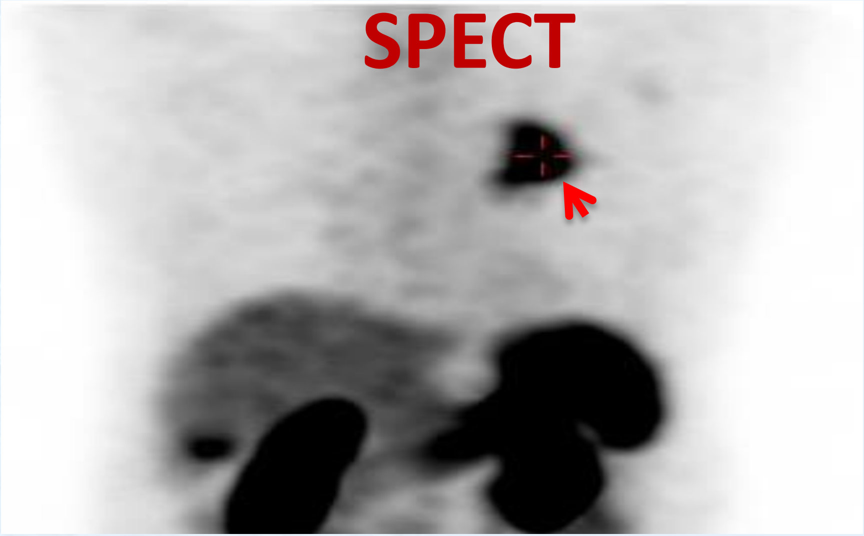


^{18}F-FDG



^{99m}Tc-3PRGD2

注：黄色箭头为炎性淋巴结显影；红色箭头为肿瘤显影

多中心临床研究

J Nucl Med. 2012, 53(5):716-722

^{99m}Tc-3PRGD2 for Integrin Receptor Imaging of Lung Cancer: A Multicenter Study

Zhaohui Zhu[1], Weibing Miao[2], Qianwei Li[3], Haojie Dai[4], Qingjie Ma[5], Feng Wang[6], Aiming Yang[7], Bing Jia[8], Xiaona Jing[1], Sha Liu[1], Jiyun Shi[8], Zhaofei Liu[8], Zhoushe Zhao[9], Fan Wang[8], and Fang Li[1]

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^{99m}Tc-3PRGD2 is a new SPECT tracer targeting integrin $\alpha_V\beta_3$ receptor for detecting tumors, imaging angiogenesis, and evaluating tumor response to therapy. A multicenter study was designed to investigate the efficacy of ^{99m}Tc-3PRGD2 for the evaluation of patients with lung cancer. **Methods:** Seventy patients (51 men, 19 women; mean age ± SD, 63 ± 9 y) with a suspected lung lesion and for whom definite pathologic diagnosis was finally obtained (malignant, $n = 58$; benign, $n = 12$) were recruited from 6 centers. Whole-body planar scanning and chest SPECT were performed at 1 and 4 h, respectively, after intravenous injection of 11.1 MBq/kg (0.3 mCi/kg) of ^{99m}Tc-3PRGD2. The images were read in consensus by 6 experienced nuclear medicine physicians masked to the source, history, and pathologic diagnosis. The tumor-to-background (T/B) ratios were calculated for semiquantitative analysis. A Student *t* test was used for statistical analysis, and a *P* value less than 0.05 was considered significant. **Results:** With low ^{99m}Tc-3PRGD2 background in the lungs and mediastinum, most lung malignancies were prominent on the 1-h images (T/B ratio, 1.65 ± 0.47 for the planar imaging and 2.78 ± 1.52 for SPECT). The T/B ratios were significantly lower in the benign lesions ($P < 0.05$). The sensitivity was 88% for semiquantitative analysis and could reach 93%–97% in visual analysis when considering the volume effect, necrosis, and metastasis. However, the specificity was only 58%–67%. Most lymph node and bone metastases could also be detected. **Conclusion:** ^{99m}Tc-3PRGD2 imaging at 1 h is sensitive for the detection of lung cancer, meriting further investigation of ^{99m}Tc-3PRGD2 as a novel clinical tracer for integrin receptor imaging.

Key Words: ^{99m}Tc-3PRGD2; integrin $\alpha_V\beta_3$; lung cancer; multicenter study; SPECT

J Nucl Med 2012; 53:716–722
DOI: 10.2967/jnumed.111.098988

Since integrins were revealed as an important family of transmembrane receptors about 30 y ago, they have been widely studied and are found to play essential roles in angiogenesis and tumor metastasis because they are mainly involved in the cell–cell and cell–matrix interactions (*1*). Integrin $\alpha_V\beta_3$ is an important member of this receptor family and expressed preferentially on various types of tumor cells and the activated endothelial cells of tumor angiogenesis but not at all or very little on the quiescent vessel cells and other normal cells (*2,3*). Therefore, the integrin $\alpha_V\beta_3$ receptor is becoming a valuable target for diagnosis and treatment of malignant tumors (*4,5*).

The tripeptide sequence of arginine-glycine-aspartic acid (RGD) can specifically bind to the integrin $\alpha_V\beta_3$ receptor (*6,7*). Accordingly, a variety of radiolabeled RGD-based peptides have been developed for noninvasive imaging of integrin $\alpha_v\beta_3$ expression via PET or SPECT (*8–17*). Among all the RGD radiotracers studied, 2 PET agents, ^{18}F-galacto-RGD and ^{18}F-AH111585, have been well investigated in clinical trials. The results demonstrated that both radiotracers allowed the specific imaging of various types of tumors, and the tumor uptake correlated well with the expression of integrin $\alpha_v\beta_3$ in both animal models and patients (*9–14*). The ^{99m}Tc-labeled RGD peptides for SPECT are rarely studied, and fewer peptides have been translated into clinical use. ^{99m}Tc-NC100692, a ^{99m}Tc-labeled cyclic peptide that contains a monomer RGD tripeptide sequence, has been proved potentially feasible for detection of breast and lung cancers in human beings (*16,17*). Recently, series of ^{99m}Tc-labeled RGD dimeric

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Published online Apr. 12, 2012.

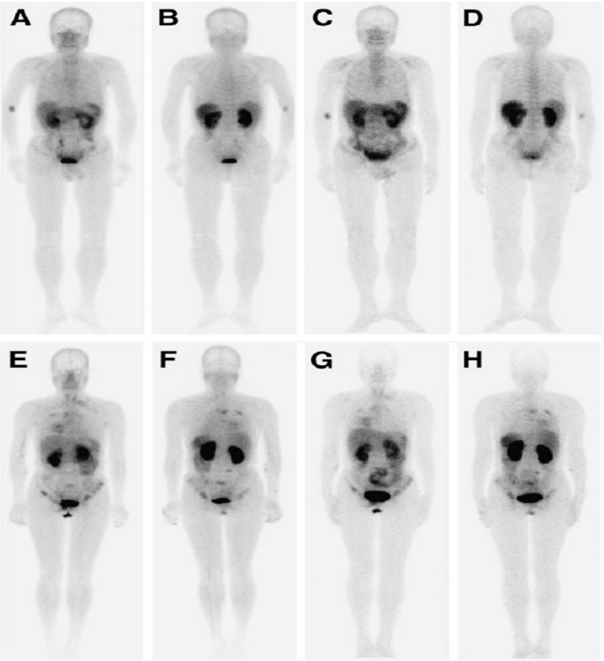

FIGURE 1. Negative and positive whole-body scans of ^{99m}Tc-3PRGD2. (A–D) Anterior and posterior whole-body images at 1 h (A and B) and 4 h (C and D) of 75-y-old man with low ^{99m}Tc-3PRGD2 uptake in chronic inflammation lesion at right upper lung (T/B, 1.1) and enlarged lymph nodes in mediastinum. (E–H) Anterior and posterior whole-body images at 1 h (E and F) and 4 h (G and H) of 57-y-old woman with lung adenocarcinoma at right middle lobe (T/B, 2.4), accompanied by mediastinal and left supraclavicular lymph node involvement and extensive bone metastases.

国际评论

Molecular Imaging
For Physicians & Executives in Molecular Imaging & Nuclear Medicine
Health Im

TOP STORIES

JNM: SPECT tracer shines light on lung malignancies

Written by Lisa Fratt
May 10, 2012

PRINT E-MAIL

FURTHER READING

Organization
- Peking Union Medical College

Person
- Zhaohui Zhu

Portals
- Molecular Imaging
- Oncology Imaging
- Thoracic Imaging
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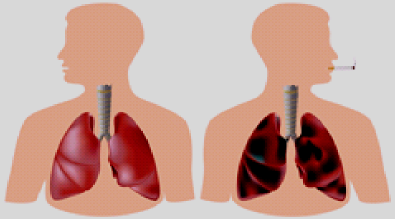
Section

^{99m}Tc-3PRGD2, a new SPECT tracer that targets integrin xvB3 receptor, is sensitive for the detection of lung cancer, according to a study published in the May issue of *The Journal of Nuclear Medicine.*



Zhaohui Zhu, MD, of the department of nuclear medicine of Peking Union Medical College in Beijing, and colleagues devised a multicenter study to examine the efficacy of ^{99m}Tc-3PRGD2 in the evaluation of patients with lung cancer. Integrin xvB3 receptor is expressed preferentially on various types of tumor cells and activated endothelial cells of tumor angiogenesis, and has emerged as a target for diagnosis and treatment of malignant tumors, according to the

SPECT显像剂在肺恶性肿瘤的诊断中显现出曙光

国际评论

中华医学会核医学分会
技术与继续教育学组

Werner Langsteger

Department of Nuclear Medicine & Endocrinology, St Vincent's Hospital, Austria

在临床上比较^{99m}Tc-3PRGD2的整合素受体显像与^{18}F-FDG/PET显像是最大的前瞻性研究，这种新型的SPECT显像剂被发现与^{18}FDG一样有效....

Eur J Nucl Med Mol Imaging (2013) 40:1438–1461
DOI 10.1007/s00259-013-2517-5

REVIEW ARTICLE

Highlights of the 25th Anniversary EANM Congress Milan 2012: nuclear medicine and molecular imaging at its best

Werner Langsteger · Mohsen Beheshti

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based SUVs from the two modalities. PET/MR with T1-weighted and T2-weighted sequences performed better than PET/CT in the anatomical correlation of the lesions (2.87±0.3 vs. 2.72±0.5; p=0.005), which was mainly a result of better allocation of the lesions in the pelvis as well as in bone (Fig. 16).In patients with elevated PSA and negative previous biopsies, ^{11}C-choline PET/MR is suitable for quantitative evaluation and might be helpful in guiding biopsy in patients with PC. More and recent data have already been published [26].

Müller et al. (Ludwigshafen, Germany) presented a high ranked paper regarding positron emission mammography (PEM) imaging in patients with breast cancer [27]. He stated that this new method would reduce the need for biopsies during clinical follow-up. Due to an intrinsic resolution of 1.6 mm, PEM showed a higher specificity (+5 %) and PPV (+14 %) than MRI in 25 patients. From the clinical point of view we could expect a reduction in the number of biopsies and re-examinations during clinical follow-up because PEM is unaffected by tumour type, hormonal status and breast density. Further details are available (NIH grant 5R44CA103102).

Jin et al. (Peking University, China) presented a comparison of ^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT for angiogenesis imaging in 42 patients with lung cancer [28]. To the best of our knowledge, this is the largest prospective study comparing clinical integrin receptor imaging with ^{99m}Tc-3PRGD2 and ^{18}F-FDG PET imaging. The new SPECT tracer was found to be as effective as FDG. All 36 malignant lung lesions were definitely detected by ^{99m}Tc-3PRGD2 SPECT/CT with tumour-to-background ratios of 5.5±3.0. Moreover, ^{99m}Tc-3PRGD2 uptake showed a good correlation with integrin $\alpha v\beta 3$ receptor expression and microvessel density. Furthermore, in the differentiation of benign from malignant lesions, FDG-positive LN were found to be negative by ^{99m}Tc-3PRGD2 SPECT/CT (Fig. 17). This new method may provide the possibility to evaluate anti-angiogenesis therapy in further studies. The most recent data have already been published [29].

Boers-Sonderen et al. (Nijmegen, The Netherlands) presented a phase I study in patients with ovarian, endometrial and breast cancer investigating the use of ^{18}F-FDG PET for the evaluation of response to treatment with temsirolimus and pegylated liposomal doxorubicin. Unfortunately, the authors did not mention the number of patients included in this study [30]. Nevertheless, they reported remarkable changes in tumour metabolism and early response rates in these tumour

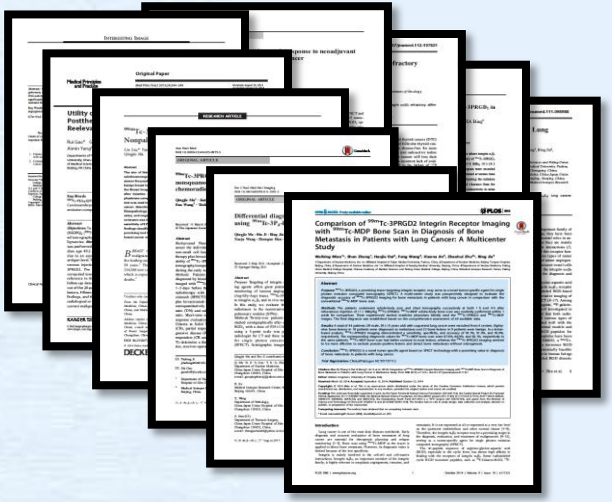
临床应用—肺癌患者

^{99m}Tc-3PRGD2 SPECT/CT and ^{18}F-FDG PET/CT in differentiation of lung lesions (79 ls) and lymph nodes (304 rs)							
Location	Exams	Positive criteria	Sensitivity	Specificity	Accuracy	PPV*	NPV *
Lung lesions	^{99m}Tc-3PRGD2 SPECT/CT	T/B>4.4	64.6%	64.3%	64.6%	82.4%	29.0%
	^{18}F-FDG PET /CT	T/B>8.0	76.9%	64.3%	74.7%	90.9%	37.5%
Lymph nodes	^{99m}Tc-3PRGD2 SPECT/CT	T/B>1.2	88.3%	94.6%	89.4%	99.2%	64.6%
	^{18}F-FDG PET/CT	T/B>1.6	90.7 %	75.0%	87.8%	94.1%	64.6%

在淋巴结转移诊断方面，^{99m}Tc-3PRGD2/SPECT比^{18}FDG/PET具有优势

Jin et al. Radiology. 2016, 281:958-966.

对本领域的贡献



- 建立了一套^{99m}Tc标记体系
- 解决了通过SPECT进行全身肿瘤检测的技术瓶颈问题
- 将使更多的中国百姓受益

不同成像技术的分辨率和灵敏度

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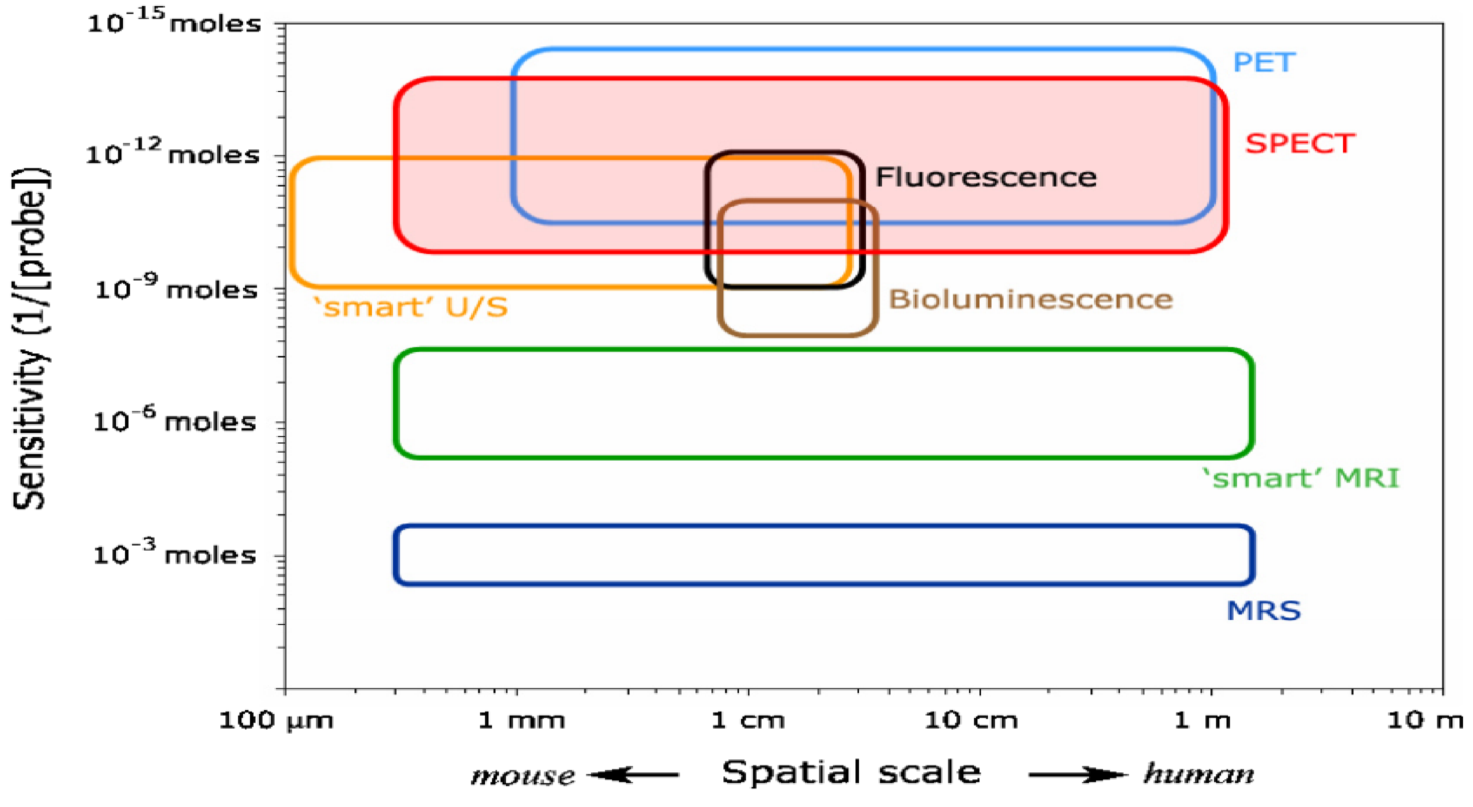
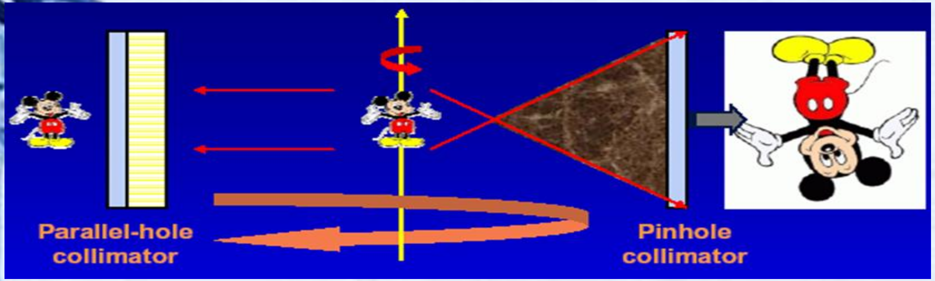


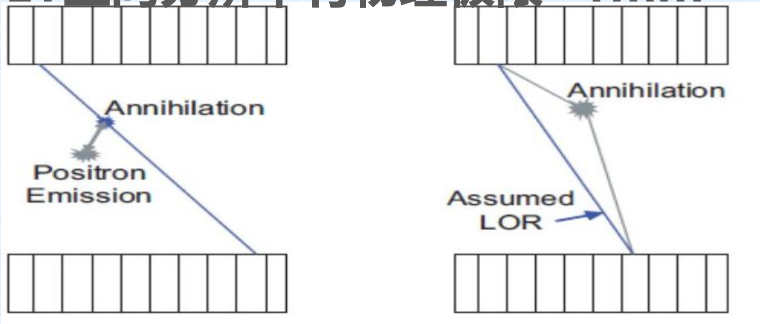
Image courtesy of S. R. Meikel et al., “Small animal SPECT and its place in the matrix of molecular imaging technologies”, Phys. Med. Biol. 50 (2005) R45-R61

SPECT与PET技术

针孔SPECT空间分辨率无物理极限



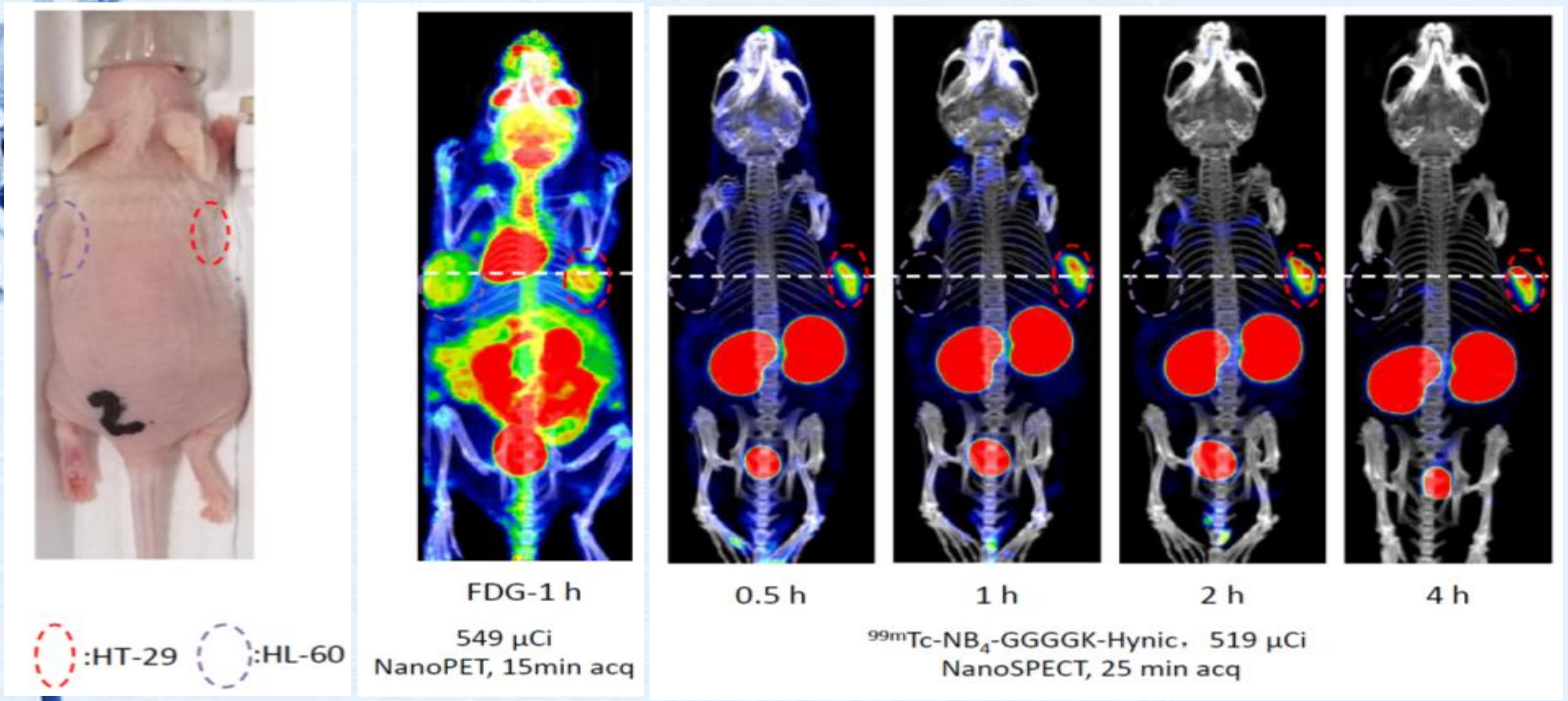
PET空间分辨率有物理极限~1mm



正电子自由程

Gamma光子对非共线性

小动物SPECT和PET显像对比



SPECT与PET

小动物

Nano SPECT/CT

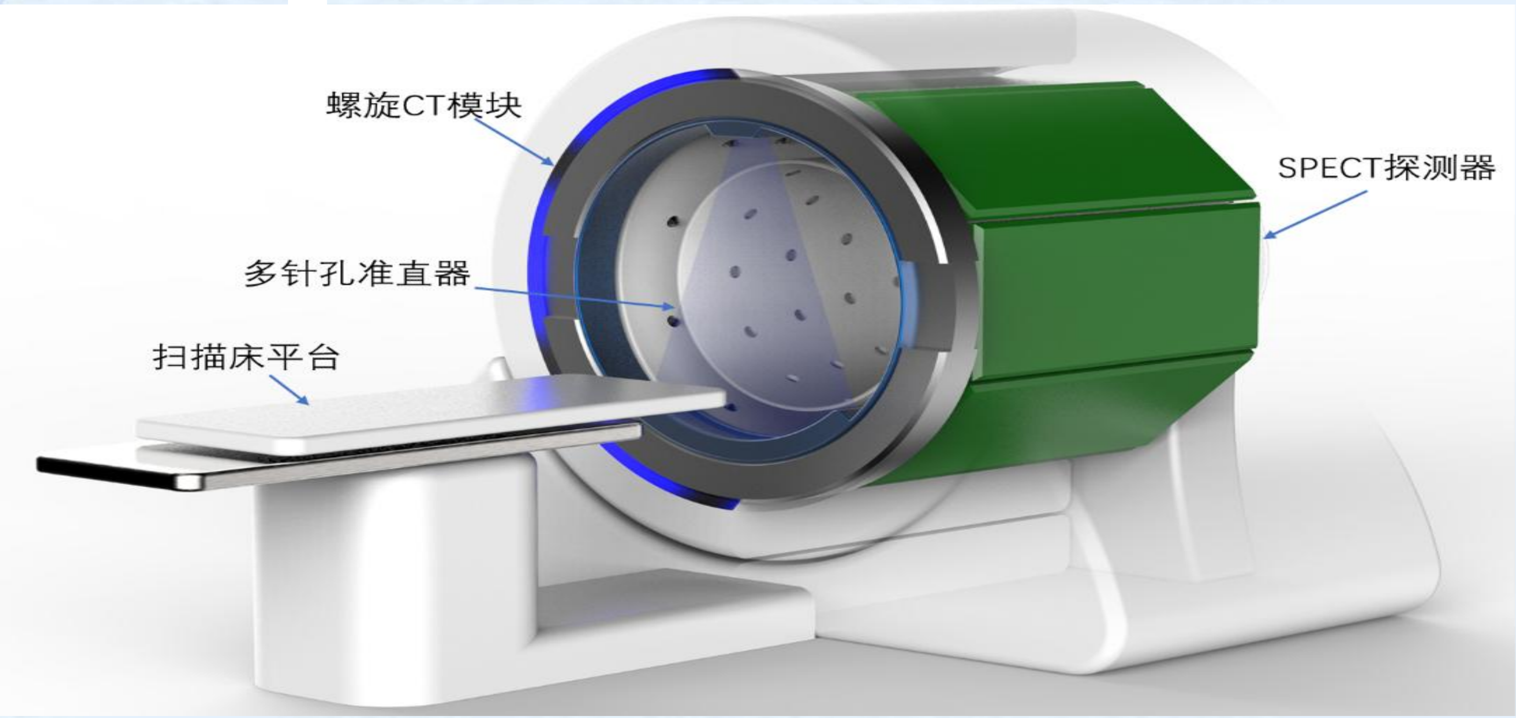
Nano PET/CT

临 床

SPECT/CT

PET/CT

全环SPECT/CT设备主体结构示意图



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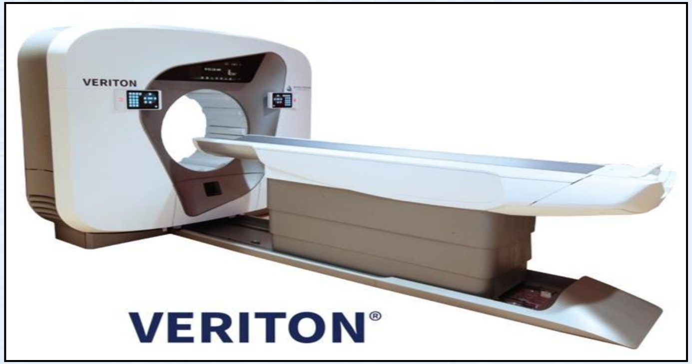
国内外现状



如果采用简单线性放大动物SPECT到高性能人体全身SPECT，则面临制造成本的巨大挑战。也就是技术上可行，但从仪器实用性和性价比的角度有重大的缺陷。

自适应成像理论

最早产生于地基天文观测领域，解决快速变化的大气环境对观测的影响。在核医学SPECT、PET及多模态成像领域，关于自适应成像的理论研究框架已经基本建立,并针对动物成像进行了尝试。

应用自适应成像理论

自适应SPECT成像的最**核心思想**是通过设计具备自适应成像能力的准直器，针对有需要的**局部而非整体视野**实现高分辨率和高灵敏度成像，降低对系统尺寸和探测器面积的要求，从而使仪器成本控制在合理的水平

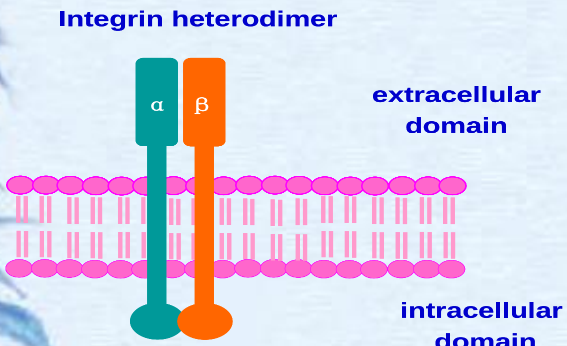
与常规设备比较

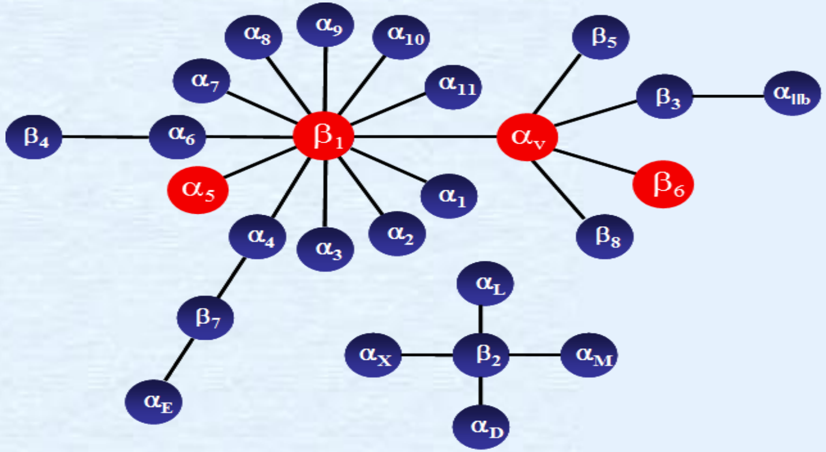
	常规SPECT	全环SPECT	PET
临床应用	肿瘤、心脑血管、甲状腺、肾、肺等		肿瘤
分辨率	10-15 mm	**< 2 mm**	3-6 mm
灵敏度	0.01%-0.02%	0.08%-0.15%	0.5%-1%
全身扫描时间	30-40分钟	10-20分钟	10-20分钟
成像方式	平扫+局部断层	**全身断层**	全身断层

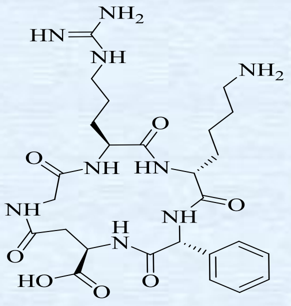
创新性

- 药物创新带动设备创新，提出“中国药-中国环”的概念。
- 提出了一套针对人体全身的多针孔准直自适应成像方案，使局部分辨率达到小于2 mm，实现临床核医学影像设备中的最优水平。
- 利用人工智能引导的自适应扫描成像，真正使人工智能技术与图像采集方法有机结合。

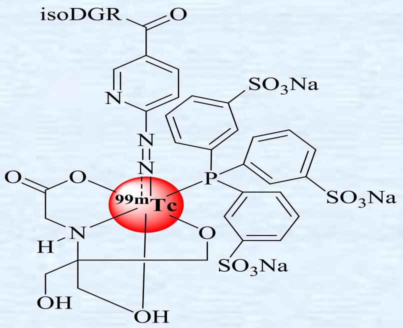
靶向integrin $\alpha_v\beta_6/\alpha_5\beta_1$的分子探针





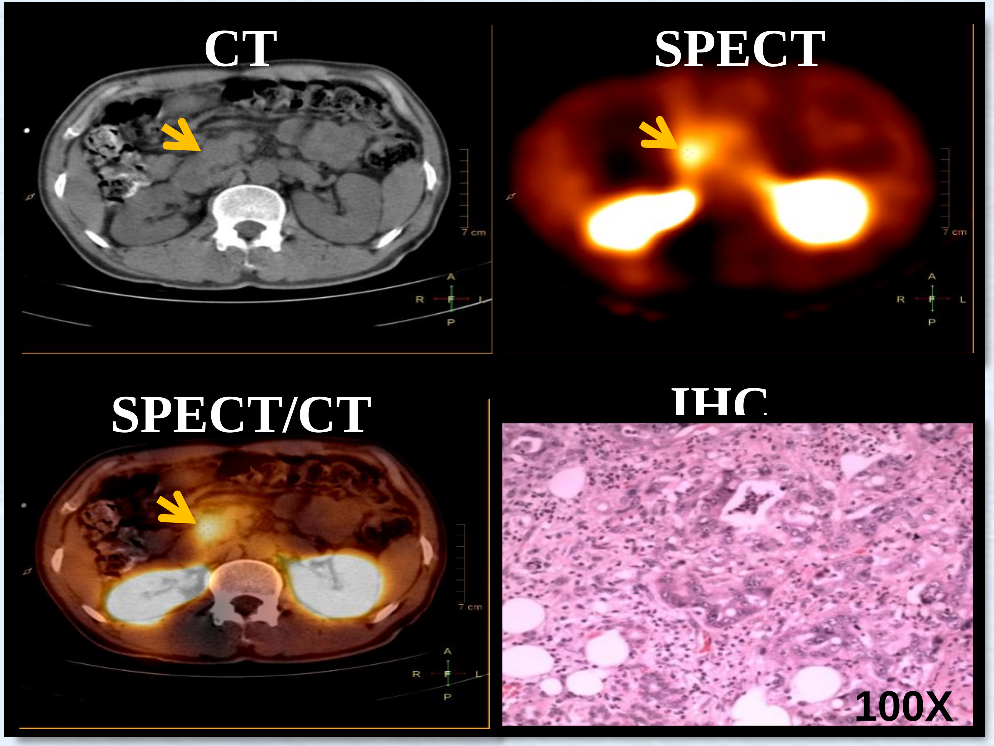


isoDGR: c(phg-isoDGRk)



^{99m}Tc-HisoDGR

靶向integrin $\alpha_v\beta_6/\alpha_5\beta_1$的分子探针



胰腺癌患者显像

Integrin α_6的表达与生存期

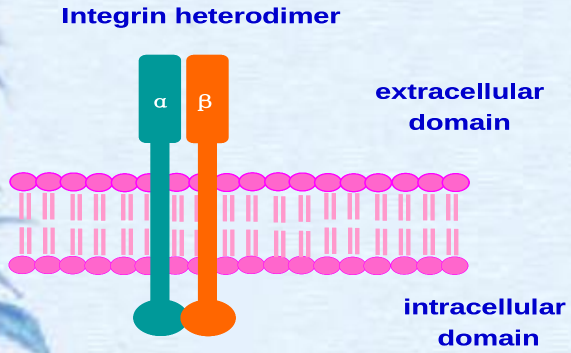
临床实验中发现，出现肿瘤远端转移的34名乳腺癌患者中，30名患者的转移灶都呈现了整合素α_6的高表达

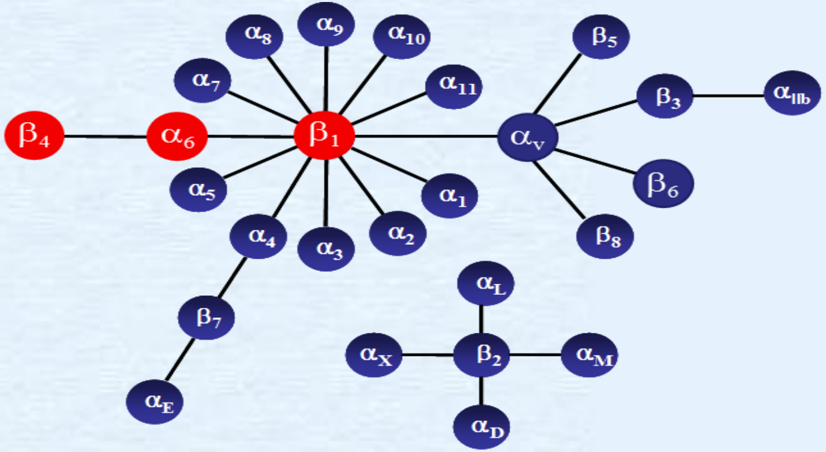
Clin Cancer Res, 1998, 4(2):407-410.

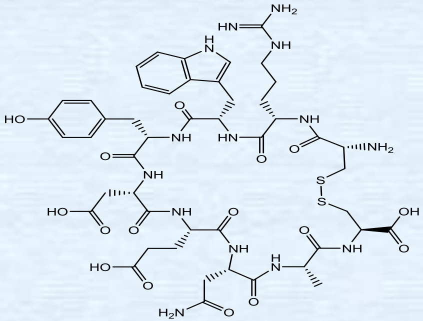
119例乳腺癌患者的临床数据中，经过手术治疗后，肿瘤整合素α_6的表达情况严重影响了患者的生存率，低表达（<5%）以及不表达整合素α_6的患者，6年的生存率是100%，而中度表达（5-75%）整合素α_6的患者，死亡率为11%，高度表达（>75%）整合素α_6的患者死亡率达到了19%

Cancer Res, 1995, 55(4):901-906.

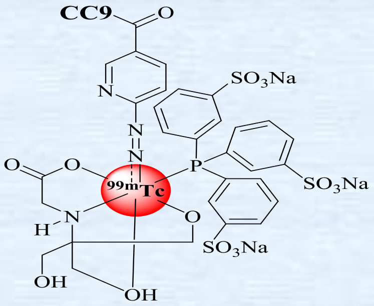
靶向integrin $\alpha_6\beta_1/\alpha_6\beta_4$的分子探针







CC9: H–C·RWY·D·E·N·A·C–OH



^{99m}Tc-HCC9

靶向integrin $\alpha_6\beta_1/\alpha_6\beta_4$的分子探针

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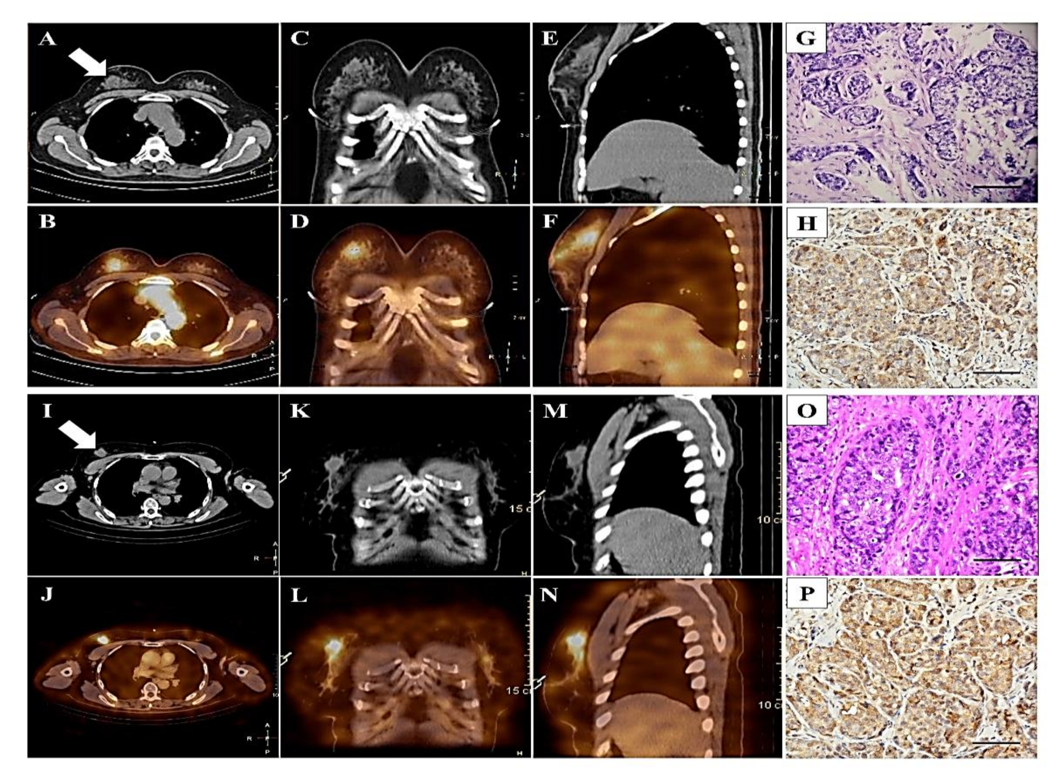
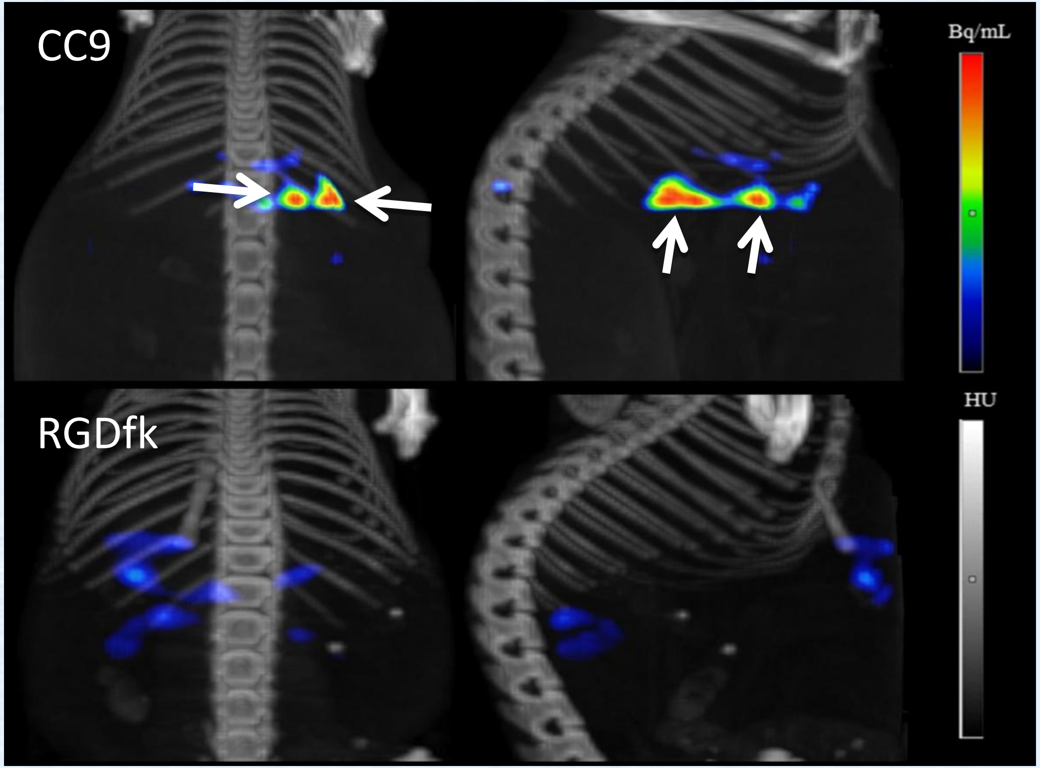


2例乳腺癌患者

靶向integrin $\alpha_6\beta_1/\alpha_6\beta_4$的分子探针



原位肝癌动物模型

PD-1/PD-L1免疫治疗

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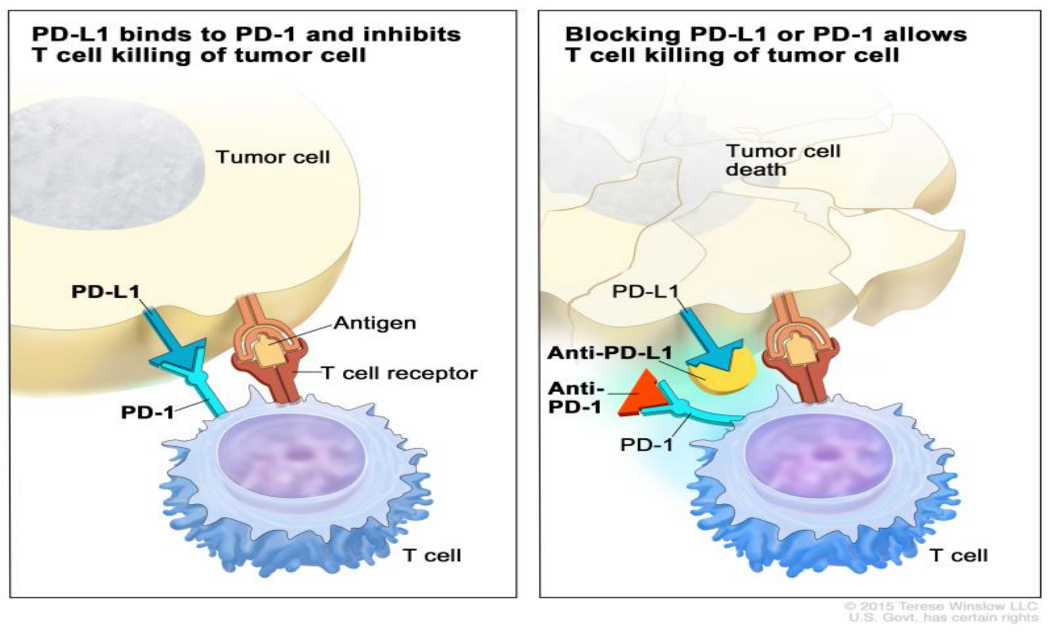

https://www.ncbi.nlm.nih.gov/books/NBK65839/figure/CDR0000258466__464/

^{99m}Tc-Nanobody (Nb17)

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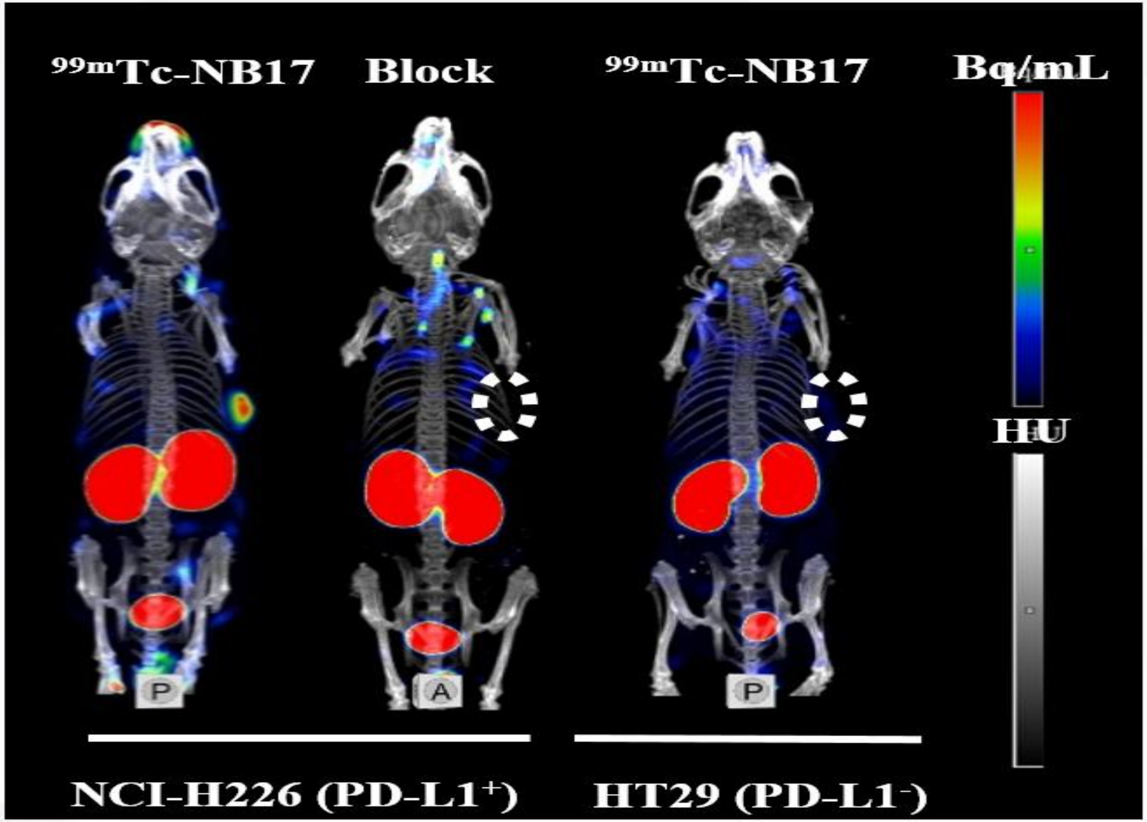

^{99m}Tc-Nanobody (MY1523)

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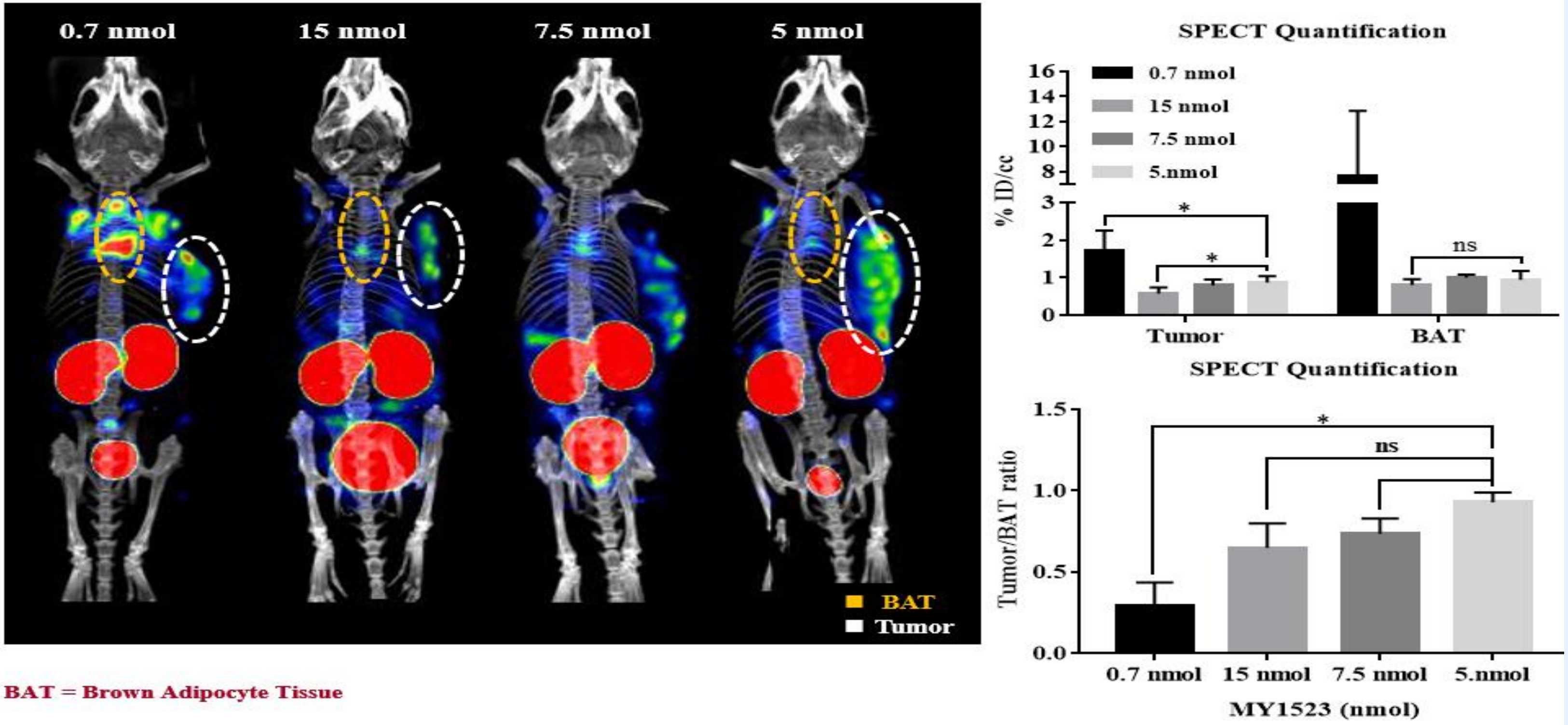
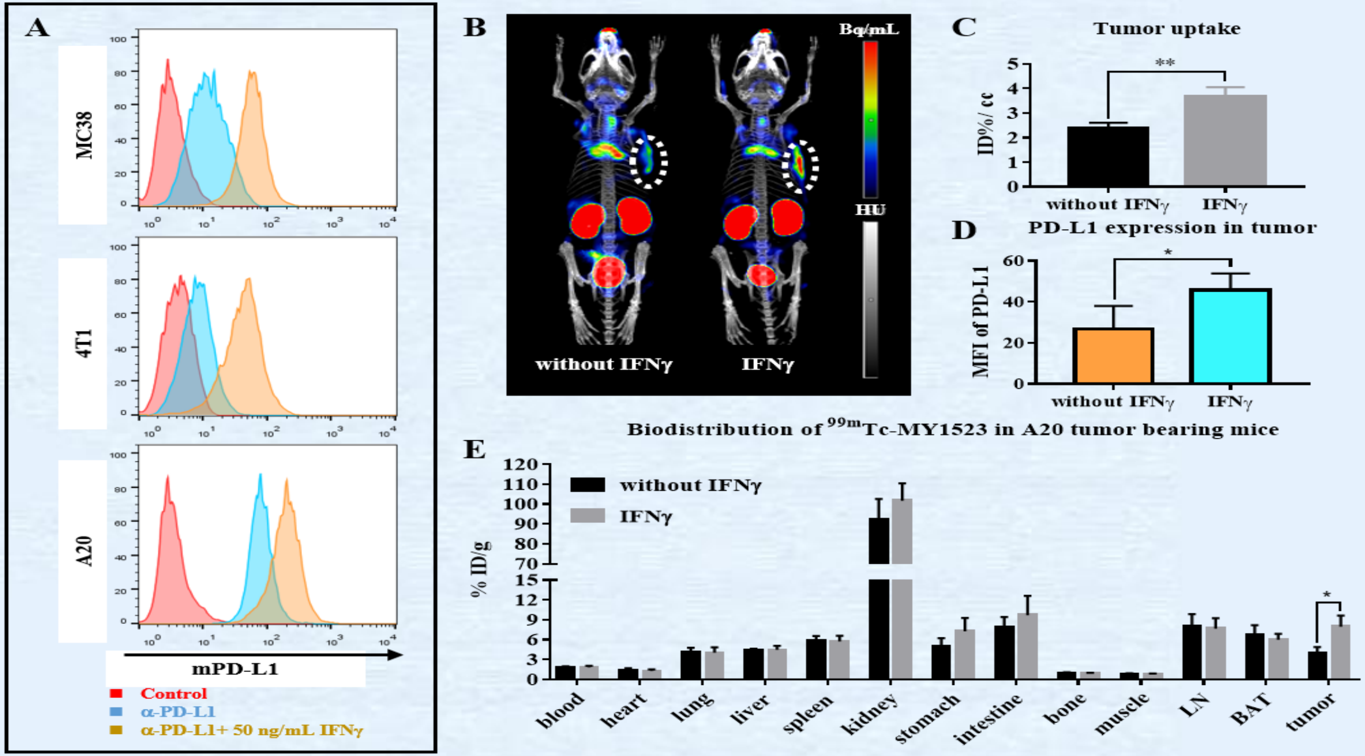
^{99m}Tc-MY1523 imaging of MC38 tumor model with different protein concentration



BAT = Brown Adipocyte Tissue

IFNγ 调控 PD-L1 表达



治疗实验计划

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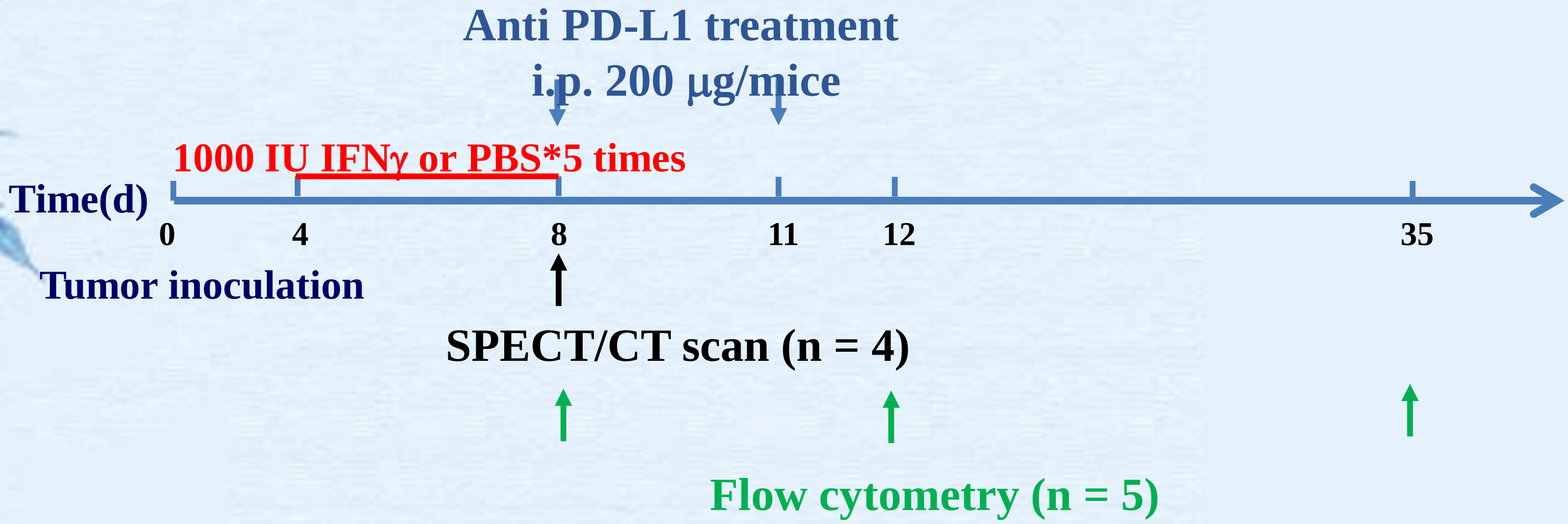
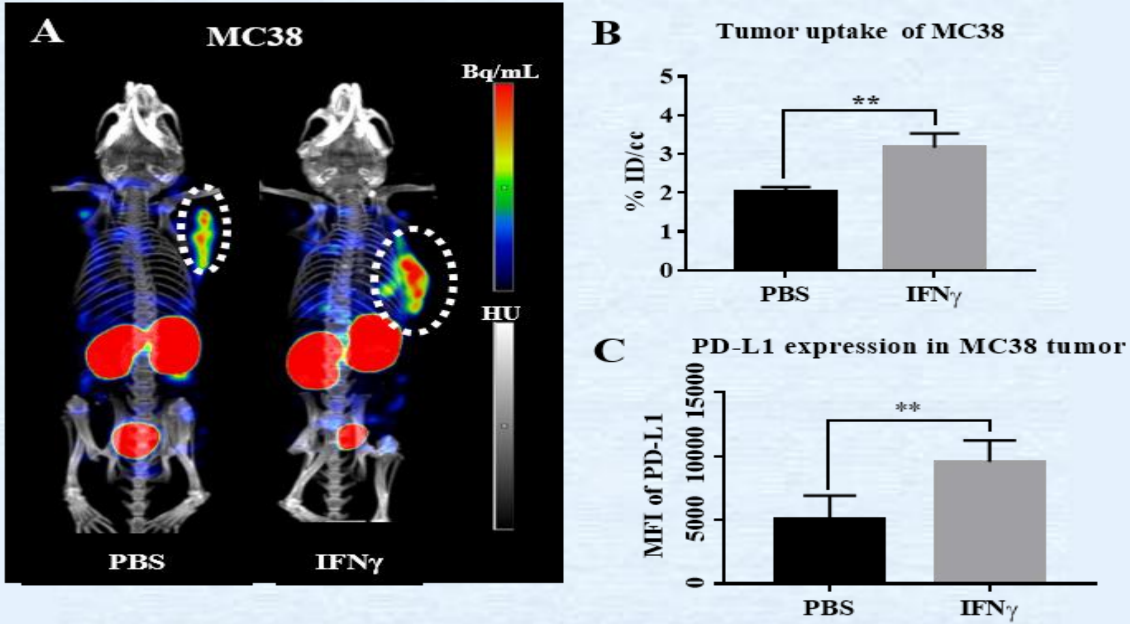


IFNγ干预后 PD-L1显像



抗PD-L1治疗

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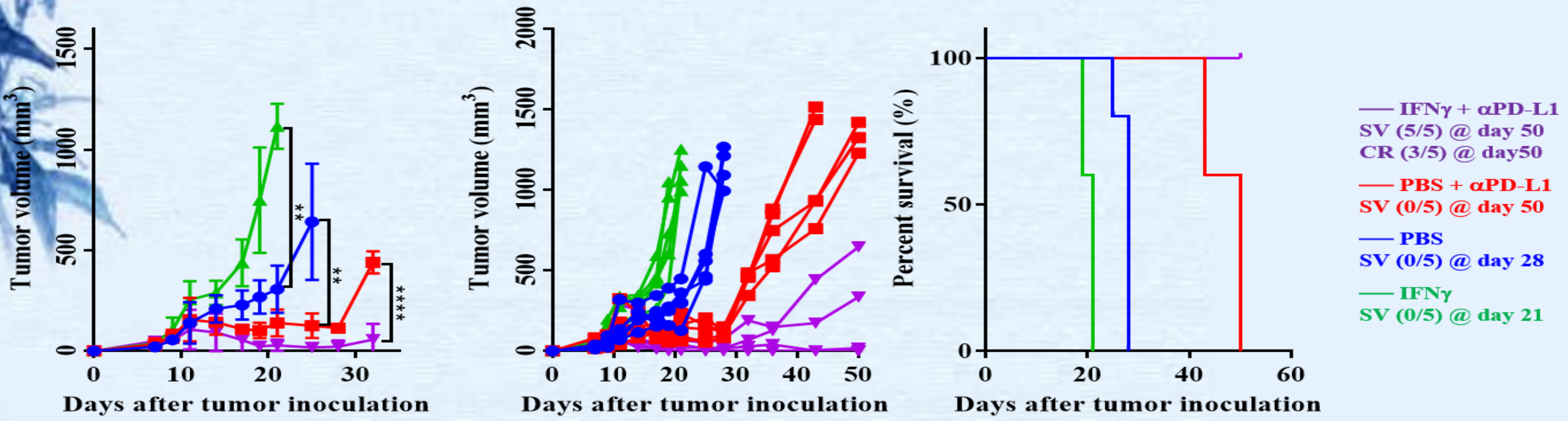
MC38 model (sensitive to αPD-L1 therapy)



SV = Survival
CR = Complete Recovery

PBS, IFNγ, αPD-L1, IFNγ + αPD-L1

核医学的明天

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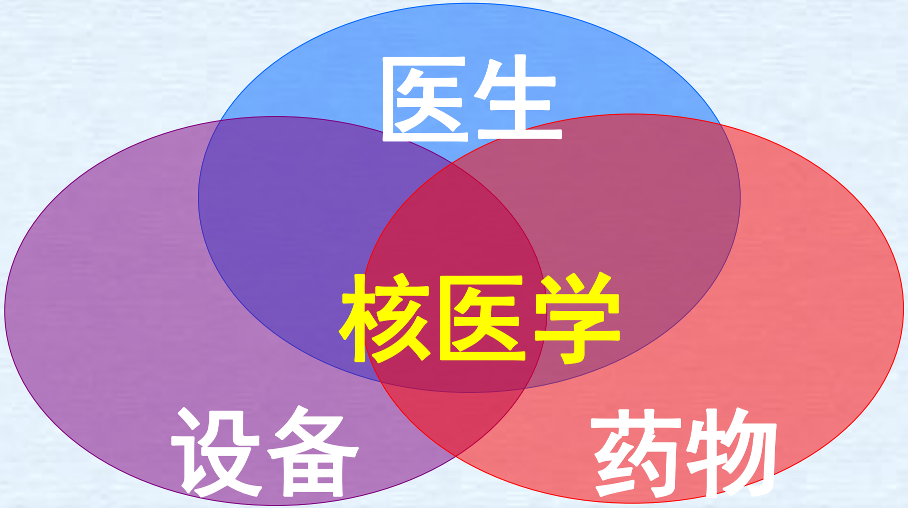

^{18}FDG/PET

^{99m}Tc-3PRGD2/Full-Ring SPECT

为癌症早筛和精准诊治提出中国解决方案

核医学的使命

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健康中国2030

癌症早诊率达到60%

癌症5年生存率提高15%

中国药—中国环

致谢

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技术与继续教育学组

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