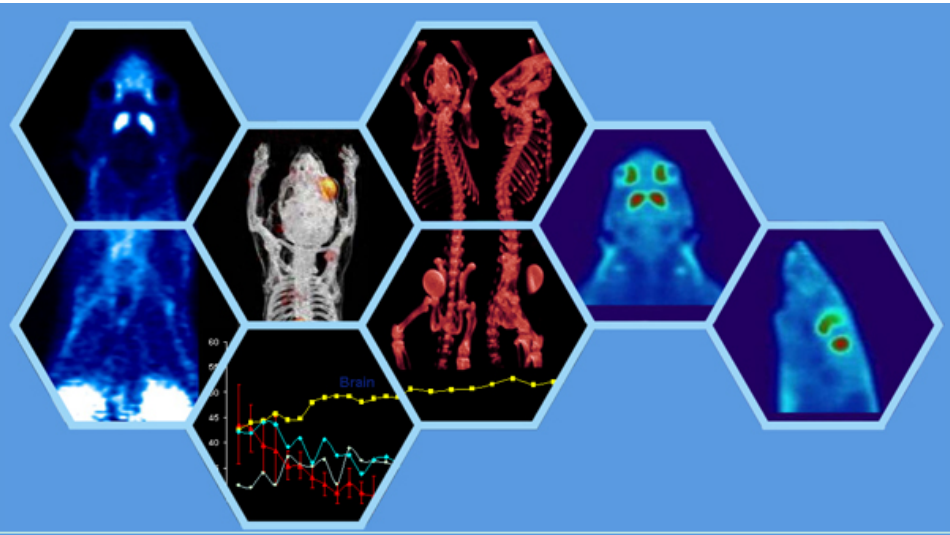
See and Treat

Molecular Imaging
Translational Research Organization

同位素示踪及分子影像技术在临床前和临床药物研究中的应用

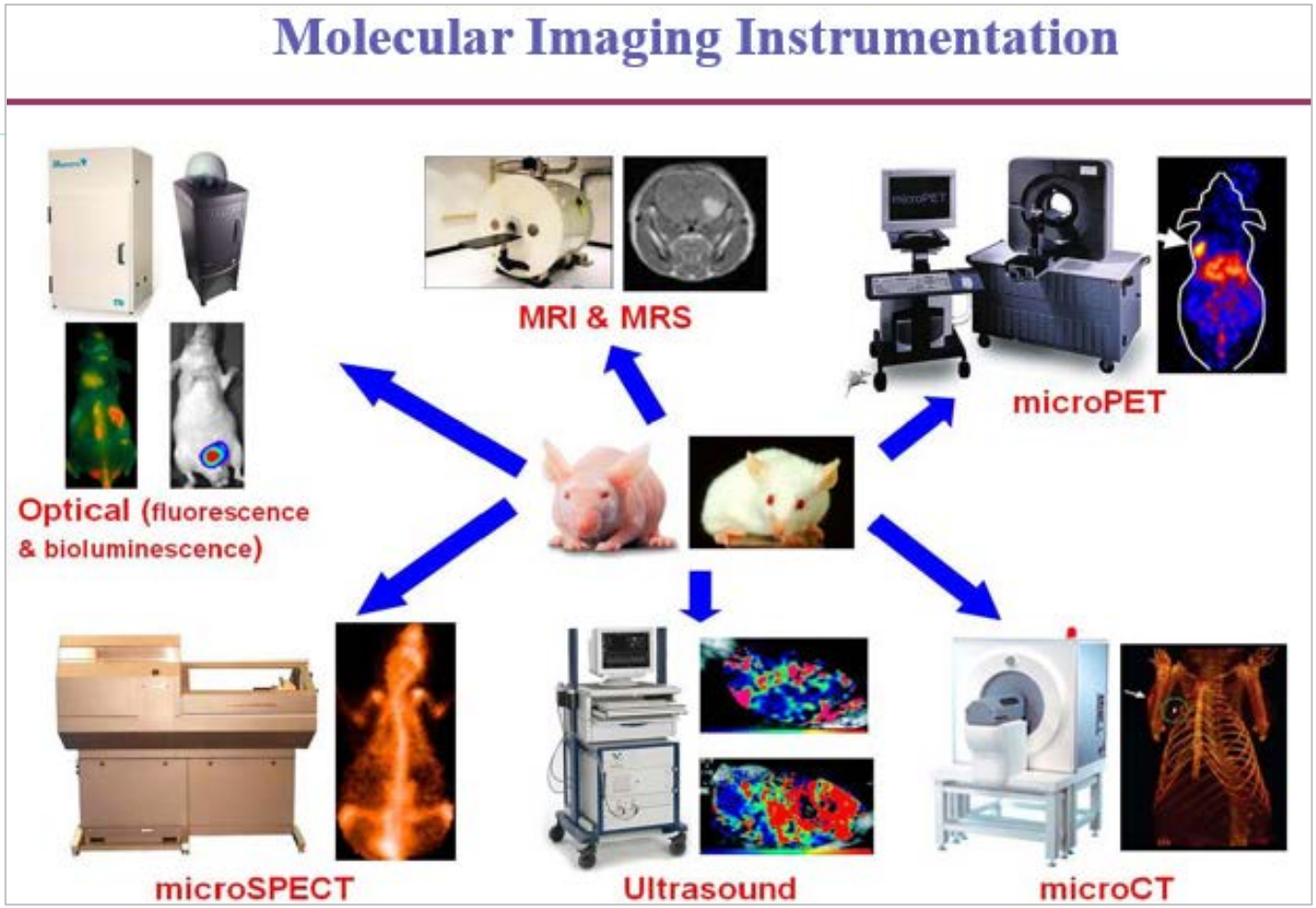
Zheng Jim Wang, PhD
MITRO Biotech. Co. Ltd.



Radioisotopes of Medical Interests

Diagnosis	***Positron emitters for PET:*** ^{11}C, ^{13}N, ^{15}O, ^{18}F, $^{60/61/62/64}Cu$, $^{66/68}Ga$, ^{82}Rb, $^{71/72/74}As$, ^{45}Ti, ^{94m}Tc, ^{89}Zr, and ^{124}I, etc. ***γ-emitters for SPECT (Single Photon Emission Computed Tomography) or gamma camera:*** ^{99m}Tc, $^{131/125/123}I$, ^{111}In, ^{67}Ga, ^{177}Lu, and ^{201}Tl, etc.
Therapy	***β-emitters (range in tissue: 0.5 – 12 mm):*** ^{90}Y, ^{131}I, ^{153}Sm, ^{67}Cu, ^{111}In, ^{166}Ho, and ^{177}Lu, etc. ***α-emitters (range in tissue: 50 – 90 μm):*** $^{212/213}Bi$, ^{225}Ac, ^{211}At, and ^{227}Th

分子影像简介



Brill DA, et al. Nanomedicine. 2015, 10, 2861-2879

Imaging modality	†Quantification	‡Required concentration	Stability	Spatial resolution
Ultrasound	Challenging	10^{-3} M	~1 h	10 mm
MRI	Excellent	10^{-5} M	Carrier-limited	0.5 mm
IR/VL	Excellent	10^{-7} M	Varies by dye	0.5–3 mm
X-ray	Challenging	10^{-5} M	3 h	50 μm
SPECT	Possible	$<10^{-10}$ M	Up to 10 days	2 mm
PET	Excellent	10^{-12} M	~2 days	1 mm

✦PET 分子影像技术

PET（Positron Emission Tomography）从分子水平上反映组织的生理、病理、生化、代谢等功能性变化和体内受体的分布情况，故也被称作“分子显像”(molecular imaging)或“生化显像” (biochemical imaging)。**能实现药物分子实时、动态、连续、活体显像追踪。**

分子细胞水平

组织学水平

药物去哪儿了？

生物分布

药物到达靶点了吗？

多少量?
什么时间?

靶点有什么东西表达？

靶点表达

药物调节靶点了吗？

功能改进

药物有效吗？

有效性

传统DMPK研究方法和技术问题

- 不能在活体获得连续多时间点血药浓度与组织分布数据
- 临床上只能获得血药浓度数据，无法同时监测人体组织药物暴露量
- 传统分析技术难以满足特殊药物及特殊用药途径的需要



Topics

- 临床前研究（Preclinical Testing）
- 临床研究（Clinical Study）
  - --临床0期研究（Phase 0）
  - --精准医疗（Precision Medicine）
- 平台概览（Platform Overview）

临床前研究（Preclinical Testing）

- 药物筛选；
- 分布及靶向性研究（单抗、ADC、细胞）；
- 药代动力学研究

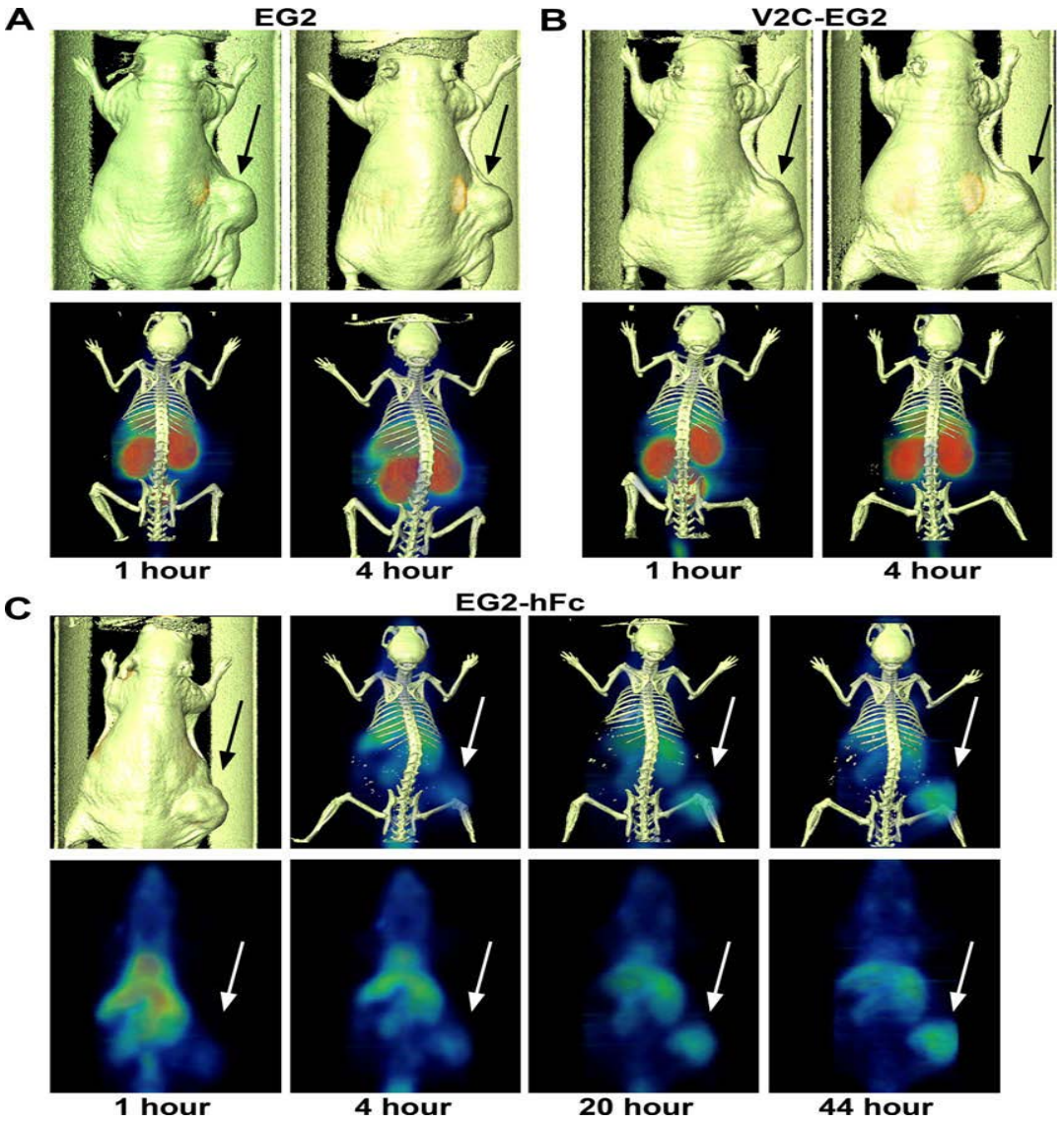
✦药物筛选

Fused microPET/CT images of human pancreatic carcinoma model MIA PaCa-2. Mice bearing established tumors were i.v. injected with

(A) ^{64}Cu-DOTAEG2

(B) ^{64}Cu-DOTA-V2C-EG2

(C) ^{64}Cu-DOTA-EG2-hFc.



Bell A, Wang Z, et al. Cancer Letters，2010, 289, 81 - 90

✦ BBB Penetration（穿透血脑屏障）

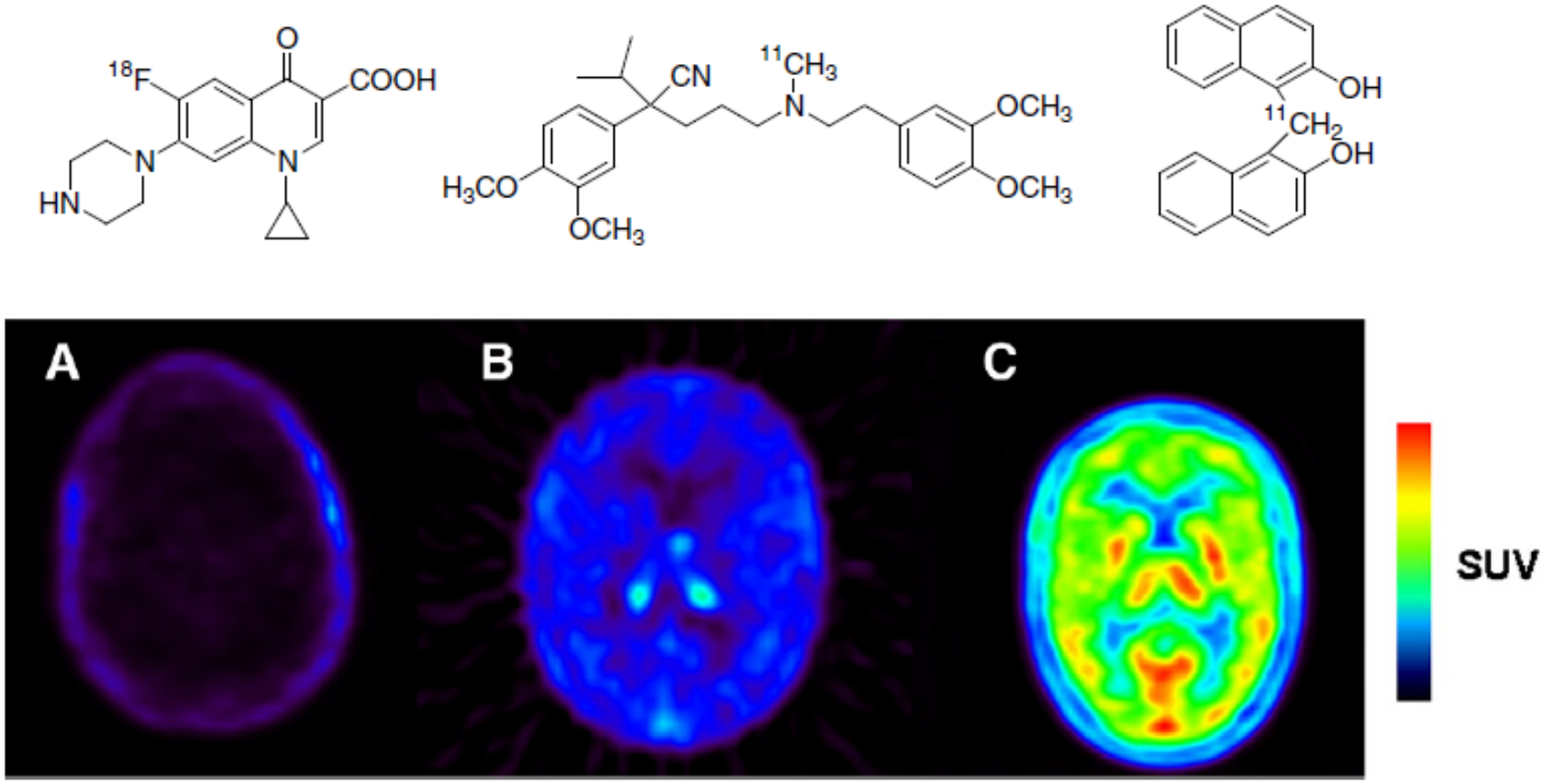


Fig. 1. Different degree of blood–brain barrier penetration of three different radiolabeled drugs revealed by PET measurements in humans (A: [^{18}F]ciprofloxacin; B: racemic [^{11}C] verapamil; C: [^{11}C]ST1859). Shown are transaxial PET summation images depicting radioactivity distribution in brain for the duration of the PET scan after iv administration of the radiolabeled drug. The radiation scale is set from 0 to 0.5 (A) and 0 to 2.0 (B, C) standardized uptake value (SUV). PET images were recorded on an Advance PET scanner (General Electrics Medical Systems). The chemical structures of each drug are shown above the PET images.

C.C. Wagner, et al, Adv. Drug Deliv. Rev. 2011, 63, 539-546

临床前研究（Preclinical Testing）

- 药物筛选；
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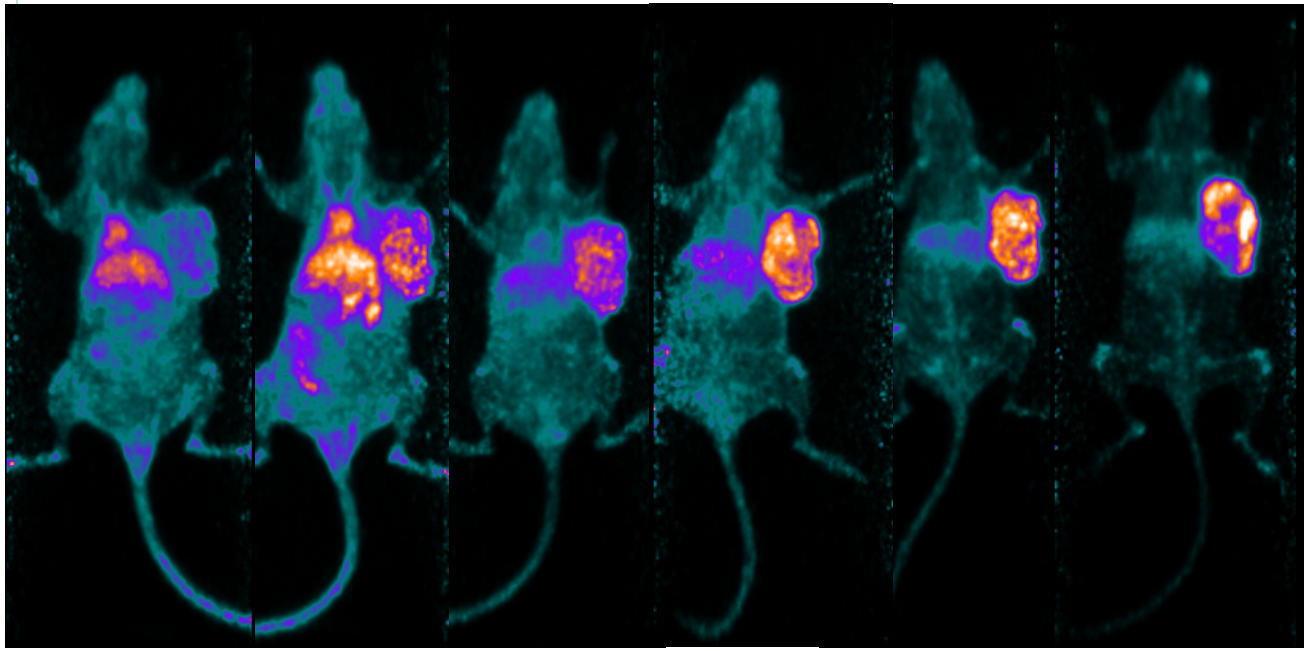
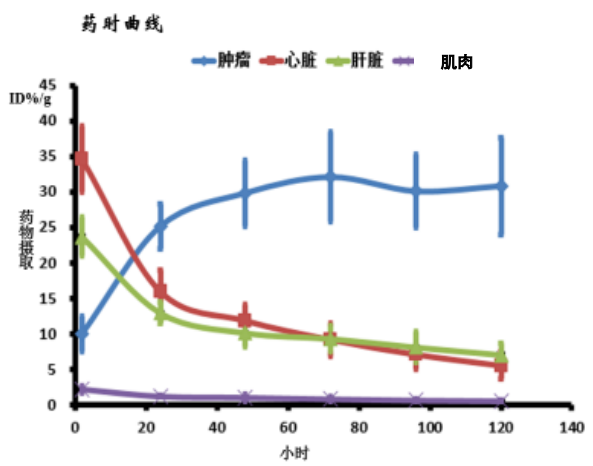
✦抗体生物分布-分子影像

Bio-distribution of anti-PD-L1 mAbs in A549 xenograft mice



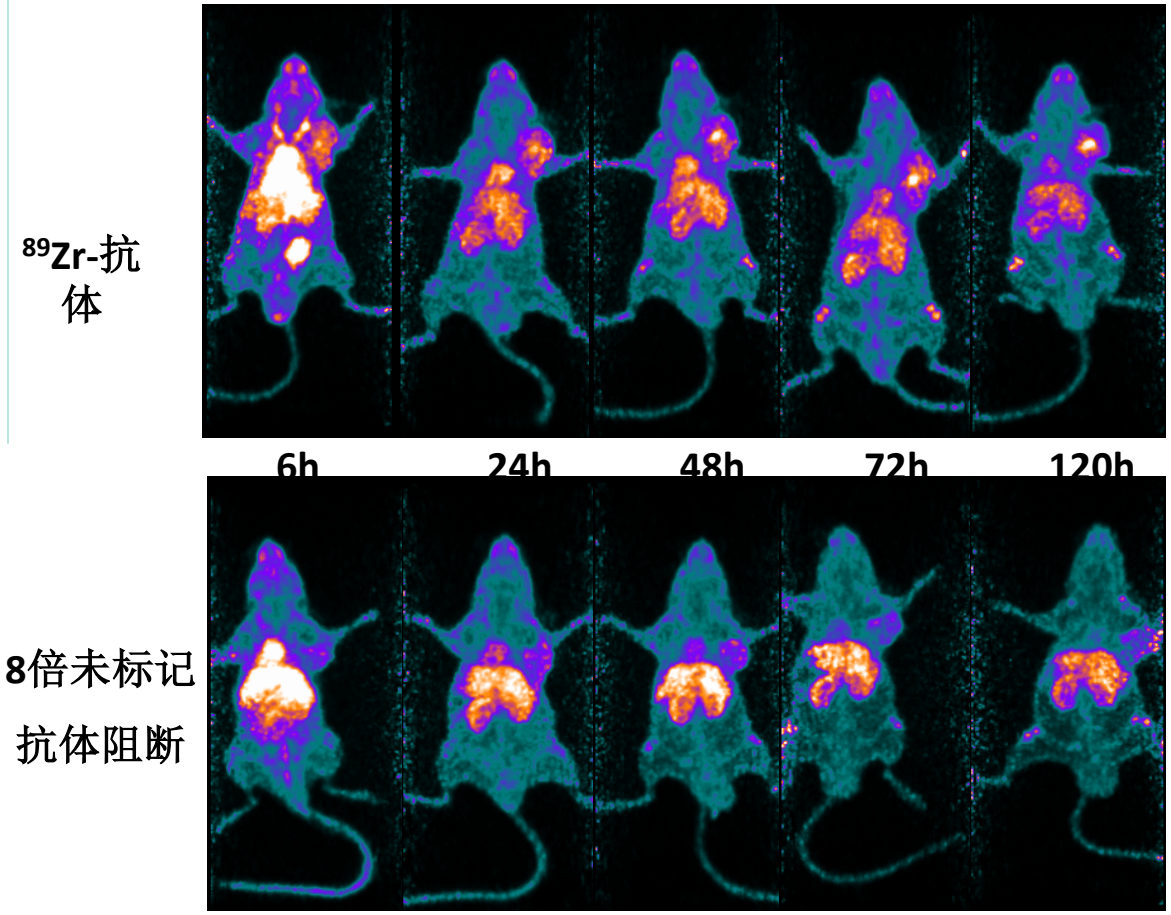
1h 6h 24h 48h 96h 120h

血药代与靶器官暴露量相关性研究

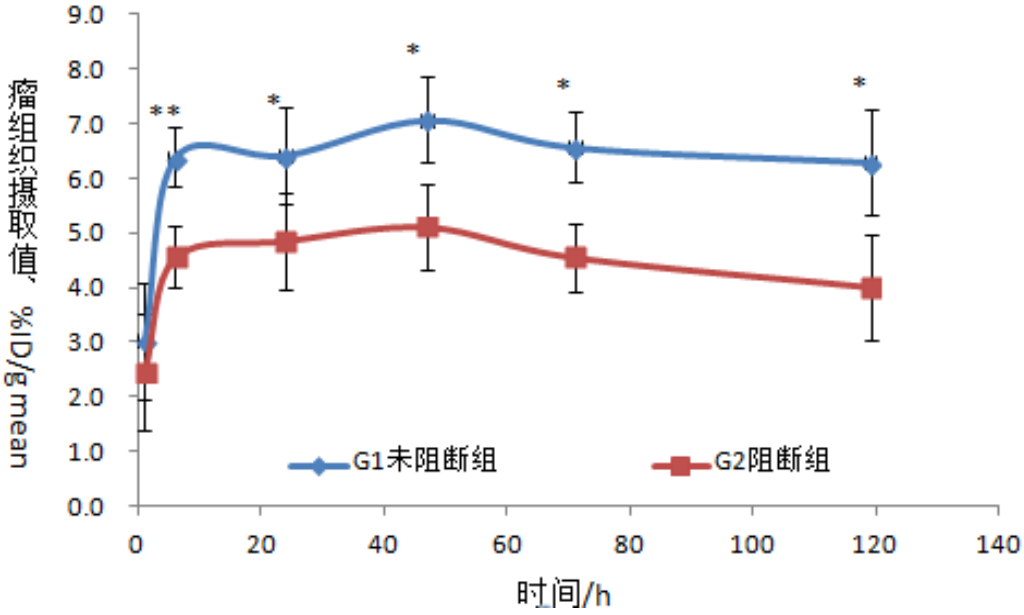


国内首个PD-L1抗体标记显像评价
已获得FDA/CFDA临床批件

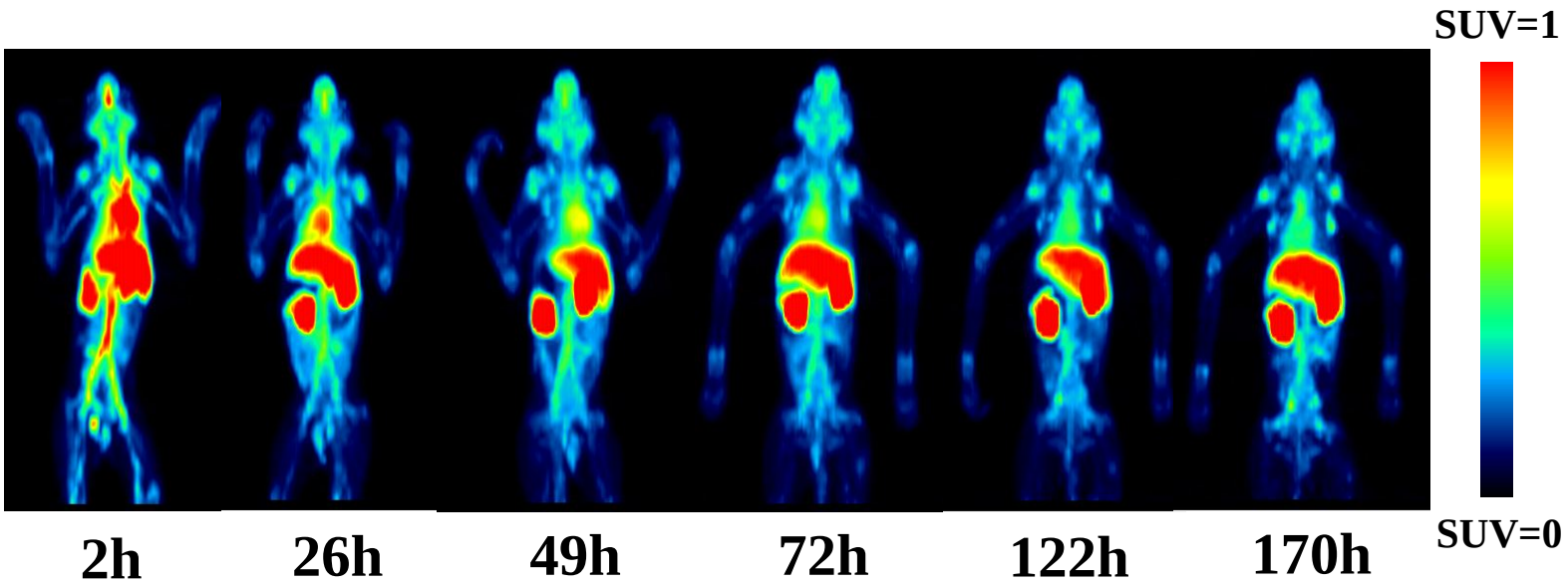
✦ Block Test（抗体靶向性验证）

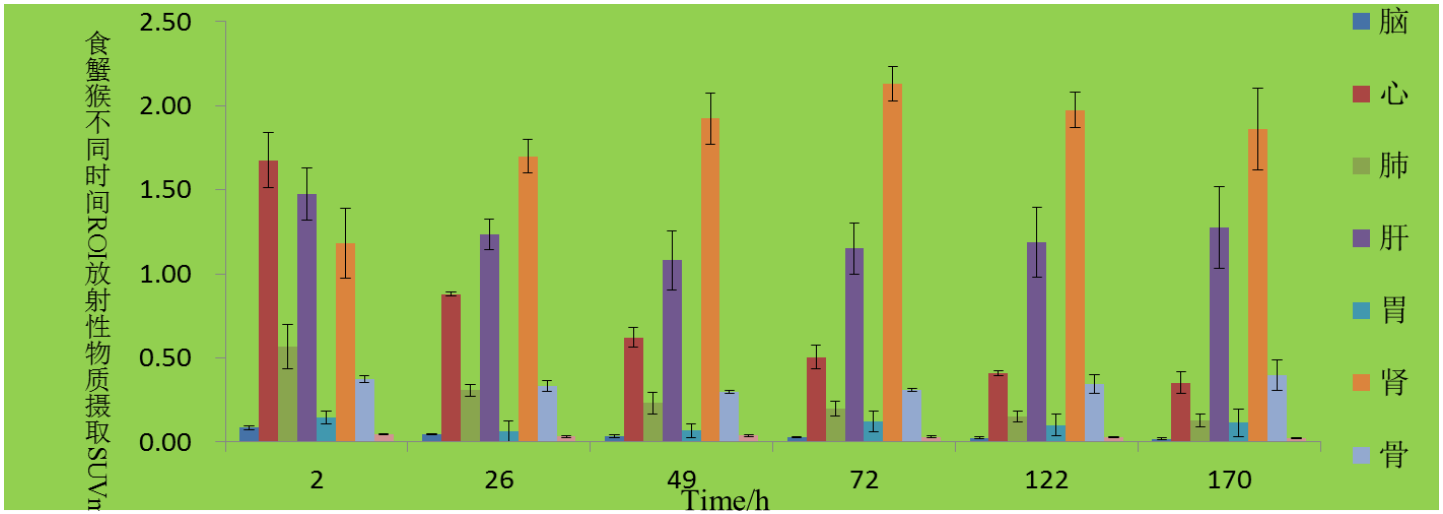


Anti-PD-L1 mAbs in A549 xenograft mice



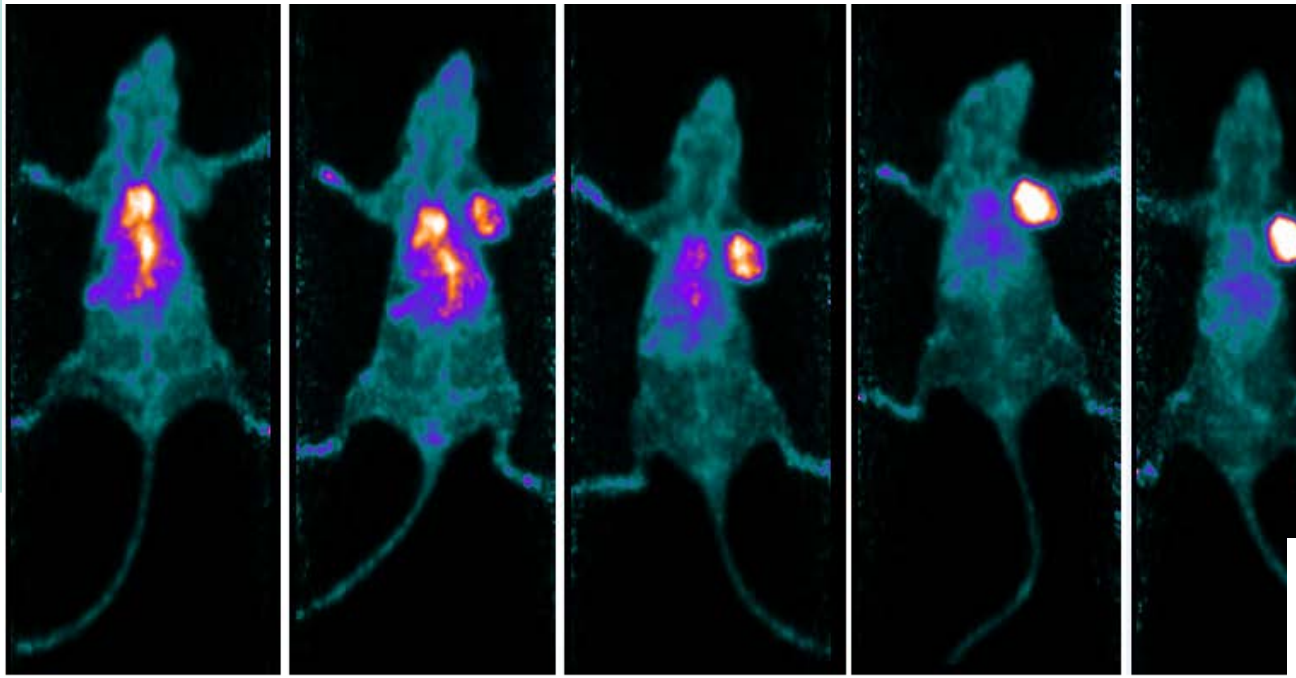
✦ 食蟹猴生物分布-分子影像

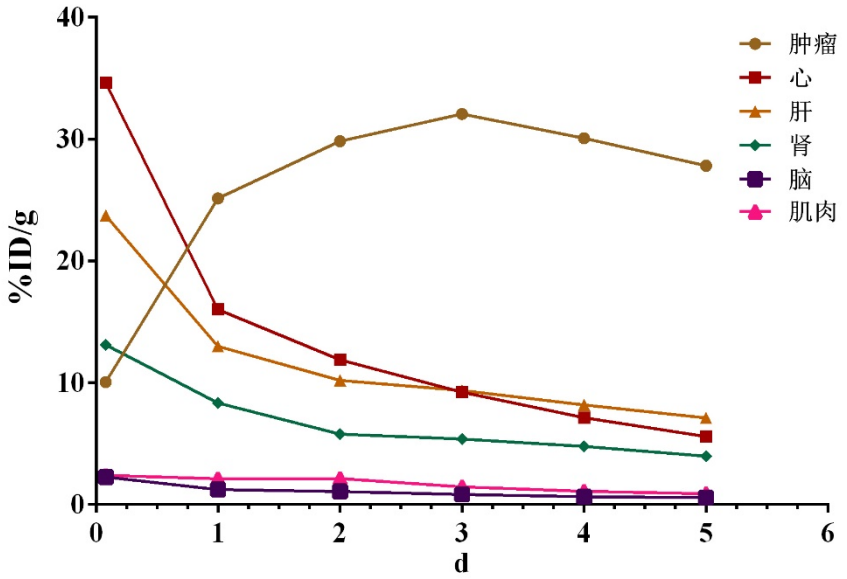




✦ ADC药物靶向分布研究

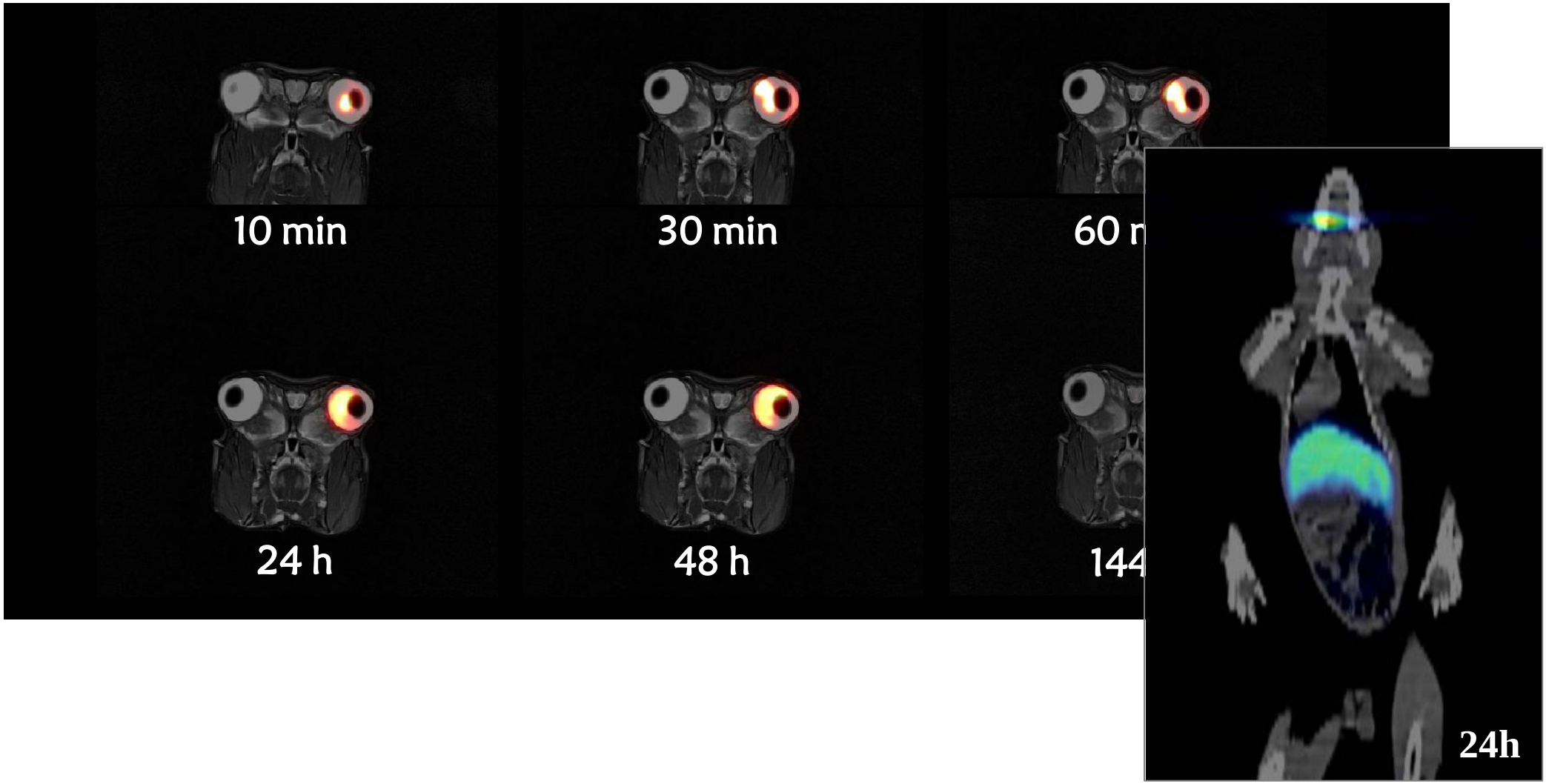
^{89}Zr-ADC（Her-2靶向）荷瘤鼠PET Imaging





✦眼科药物——生物分布

^{89}Zr-Avastin，兔子右眼玻璃体腔注射，100μCi/150μl。（PET/MRI）



✦ Cell Trafficking（细胞生物分布）

细胞制品类药物PK研究-CFDA

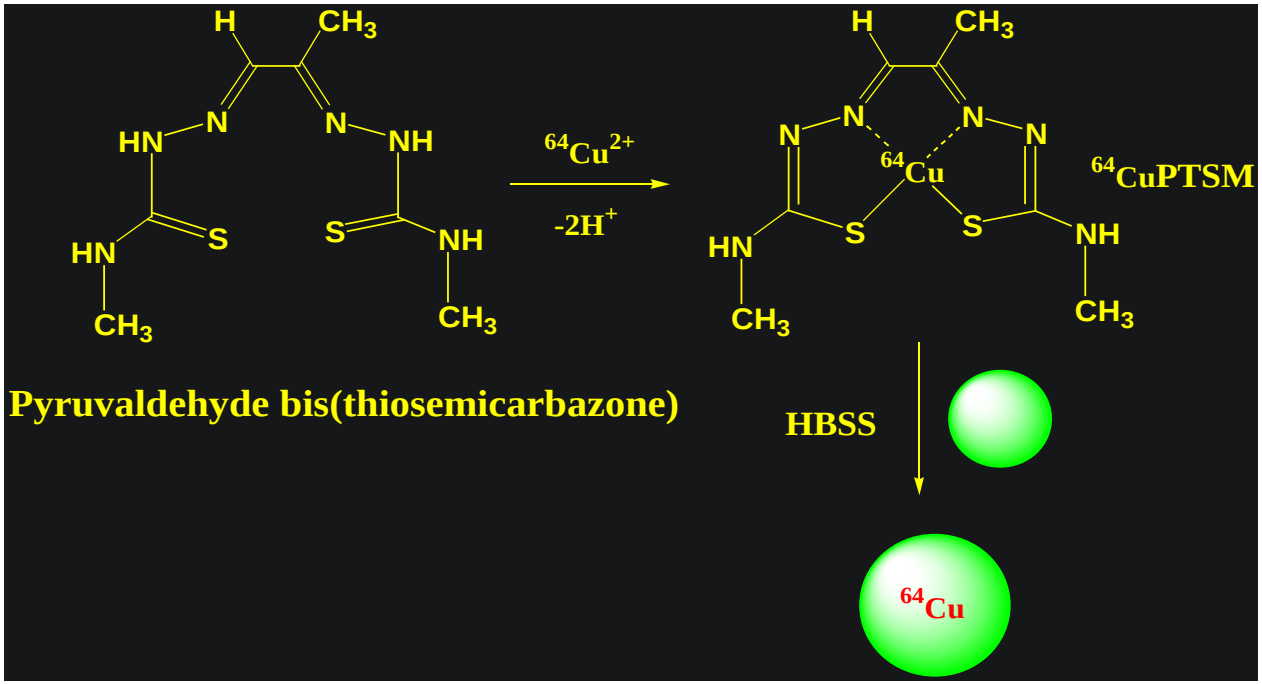
✦ 细胞制品研究与评价技术指导原则(征求意见稿)：具体问题具体分析

1. 生物分布
2. 细胞迁移、定植（归巢）、分化
3. 细胞在体内的生物学行为
4. 对于基因修饰细胞的特殊考虑

- 应采用一种或多种细胞追踪方法，并阐述方法的科学合理性。
- 可选择的技术方法有：影像技术、PCR 技术、免疫组化等。

◆ Cell Trafficking（细胞示踪）

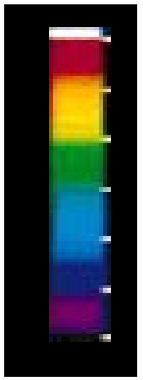
Radiolabeling of Cells with 64Cu-PTSM



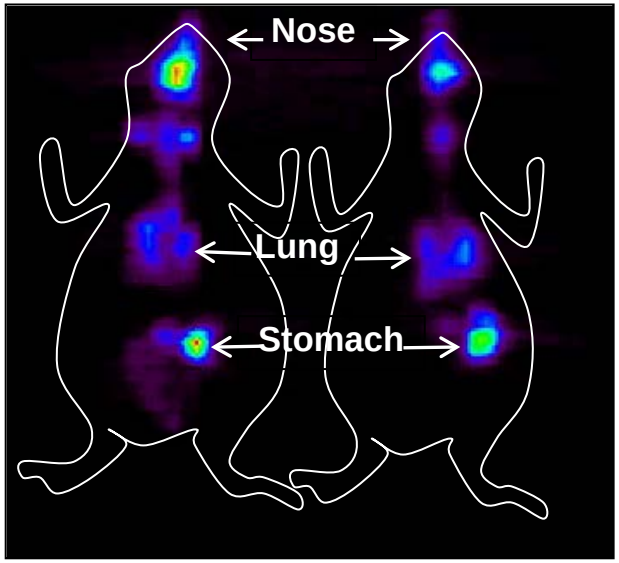
Radiolabel any type of cells, including t-cell, stem cell, bacteria, yeast, and fungus with ^{64}Cu-PTSM or ^{111}In-Oxine.

Ojeda S, Wang Z, *et al.* *BMC Microbiology , 2008, 8, 215-228.*

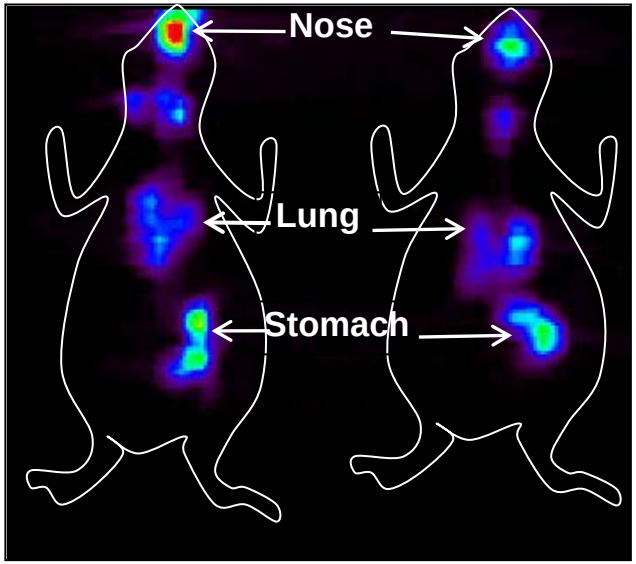
SCALE



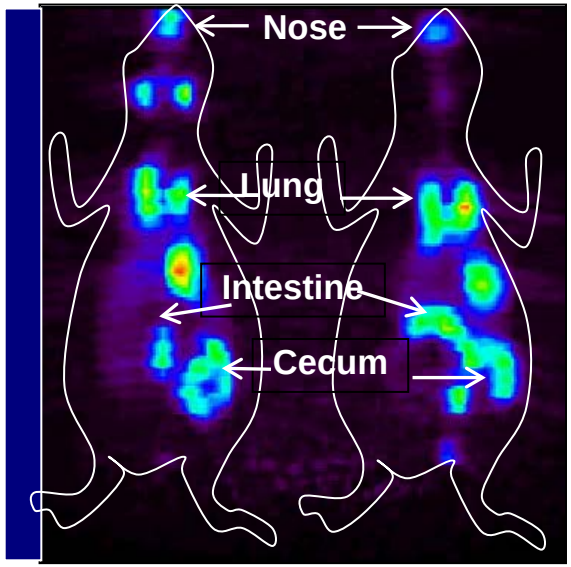
Bacteria disseminates very rapidly to the intestinal tract.



F. tul. sp. *novicida* i.n. 15 min



2 hr



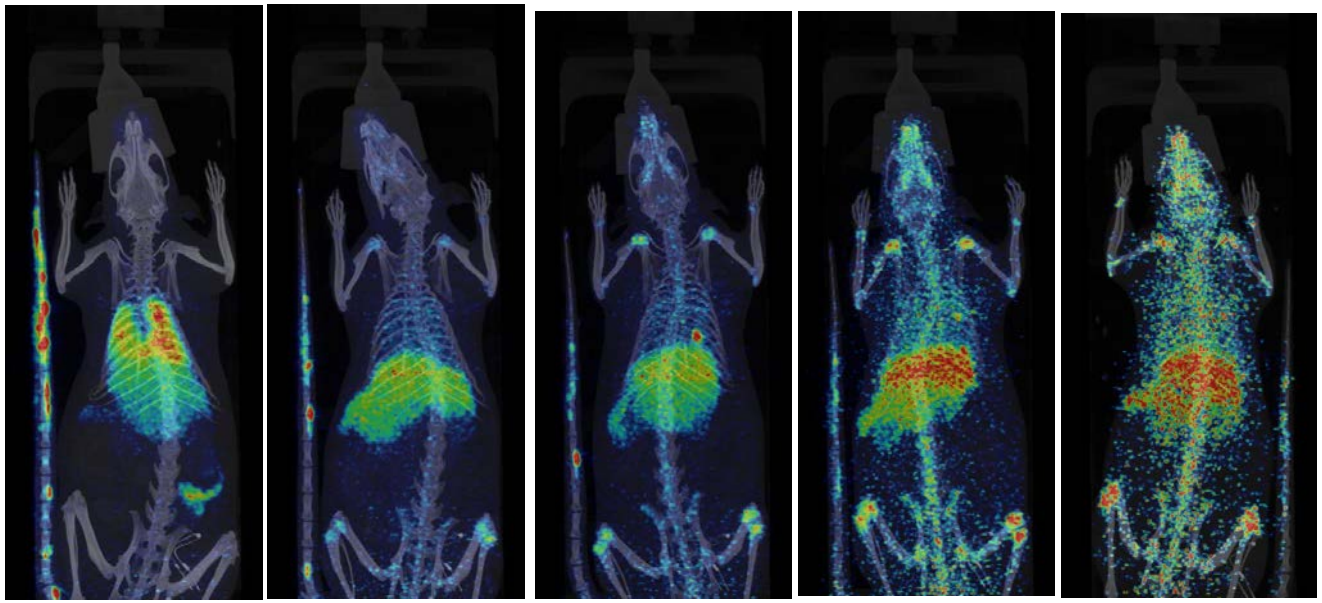
20 hr

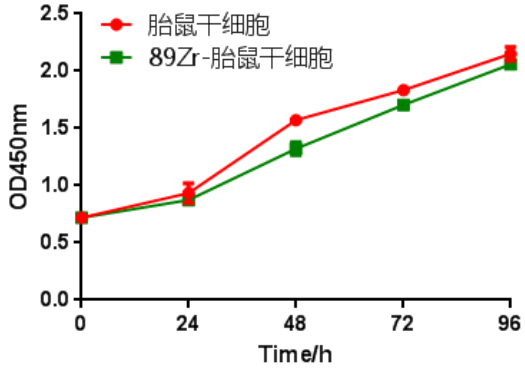
Ojeda S, Wang Z, *et al. BMC Microbiology, 2008, 8, 215-228.*

✦ Cell Trafficking（细胞示踪）

直接标记

^{89}Zr-细胞小动物PET/CT扫描图



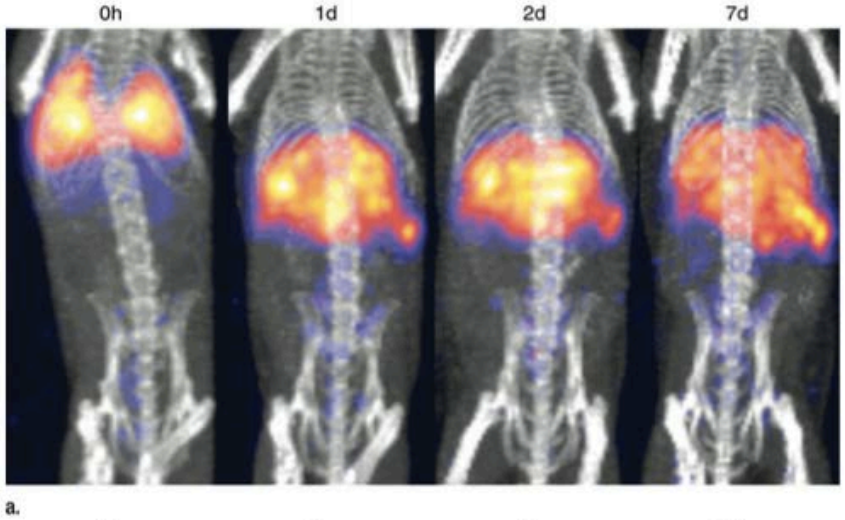


- 活体与离体方法相结合
- 活体：PET方法
- 离体：伽马计数；PCR

✦ Cell Trafficking（细胞示踪）

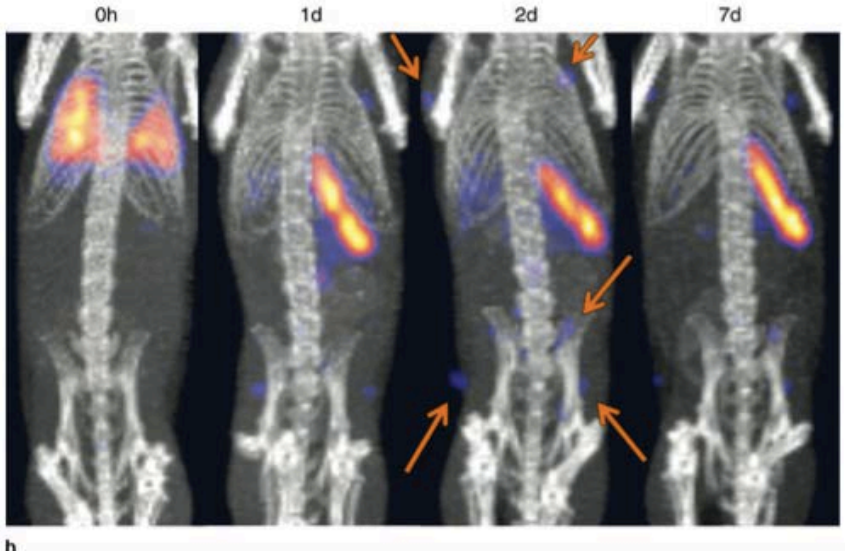
^{89}Zr-Oxine 树突状细胞（DC）/ 细胞毒性T淋巴细胞（naive CTL cell）

DC cell



DC细胞从肺至肝，最后到脾

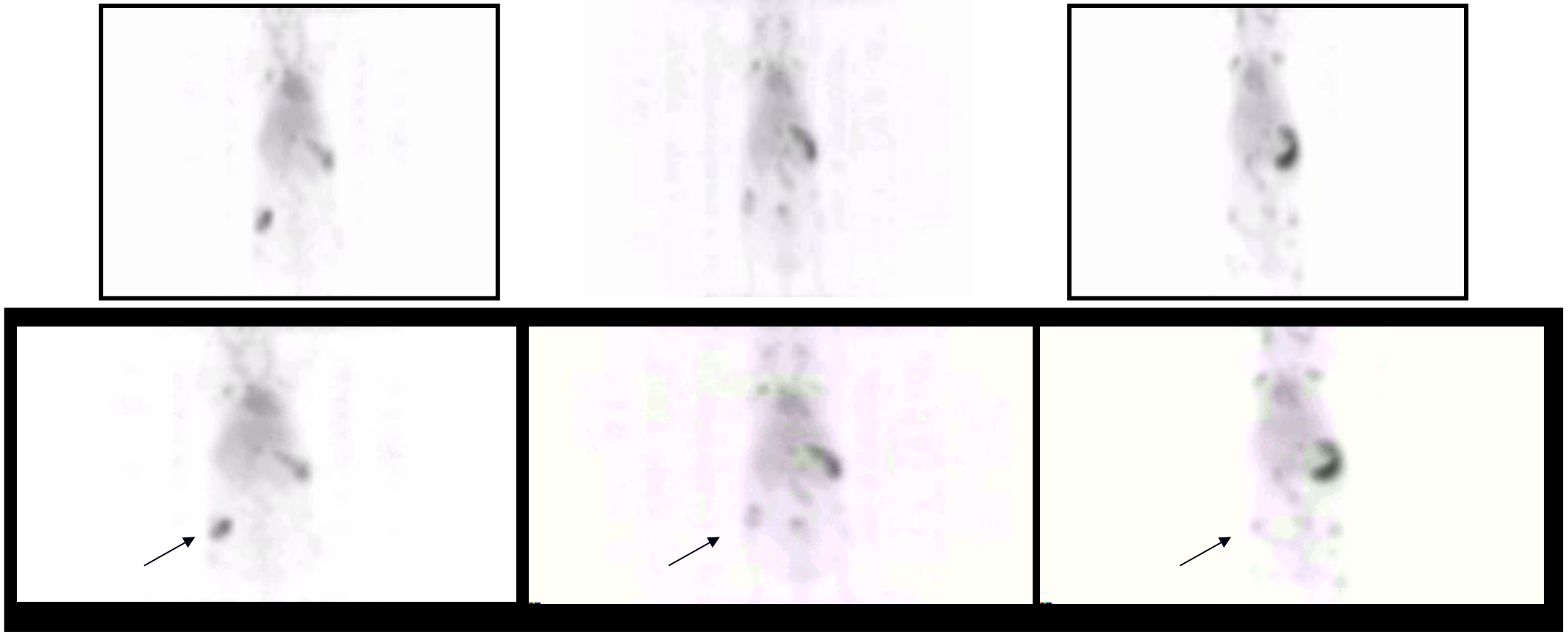
Naive CTL cell



T细胞归巢于脾脏和淋巴结

Noriko Sato,Radiology:, Jan 28 ,2015

免疫T细胞治疗肿瘤分子影像研究

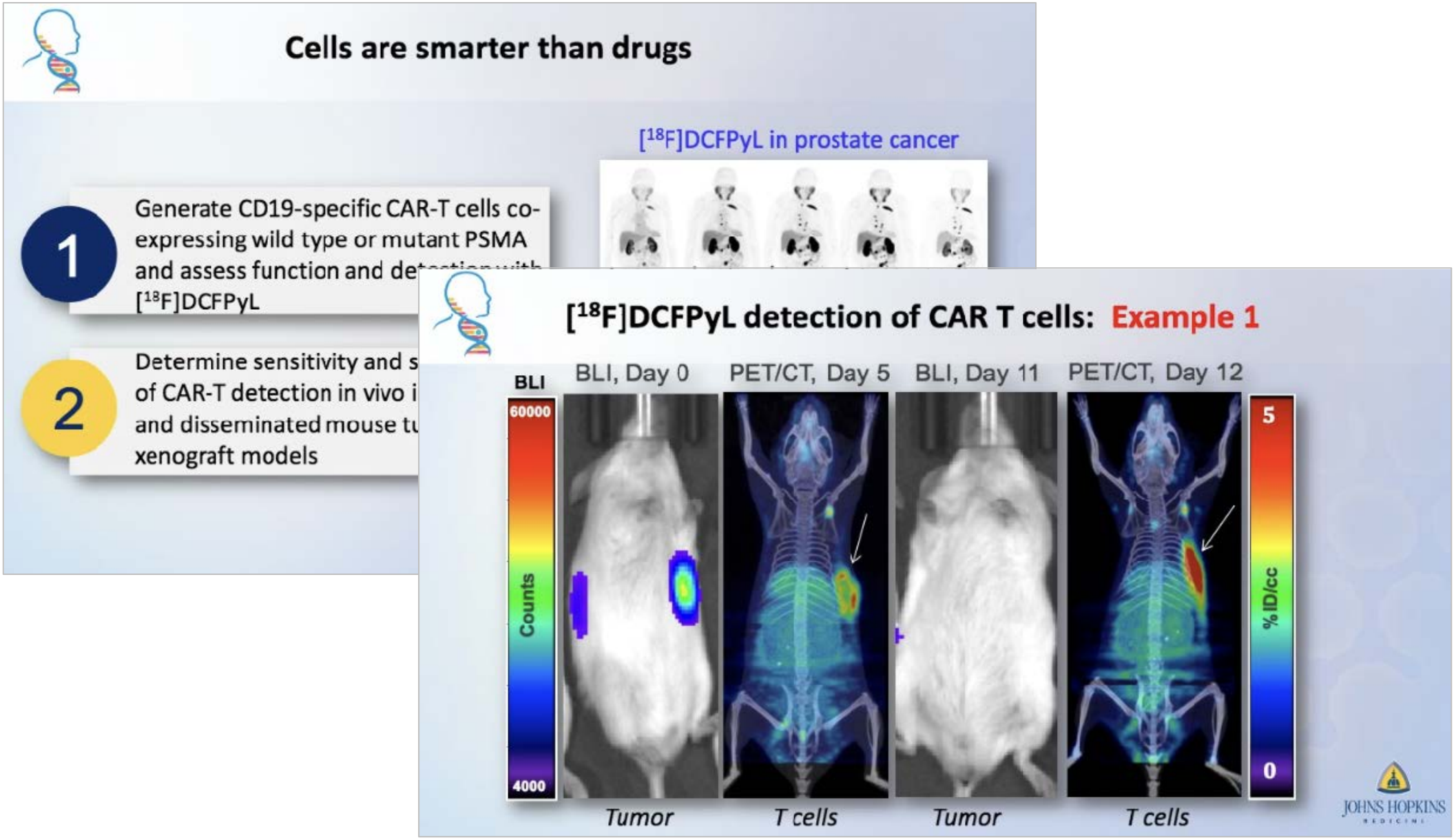


4 days - treatment **8 days - treatment** **15 days - treatment**

Wipke BT, Wang Z, et al. ***Nature Immunology, 2002, 3, 366-372.***
Matsui K. Wang Z, et al. ***Nucl Med & Biol, 2004, 31, 1021-1031.***

✦ Cell Trafficking（细胞示踪）

间接标记

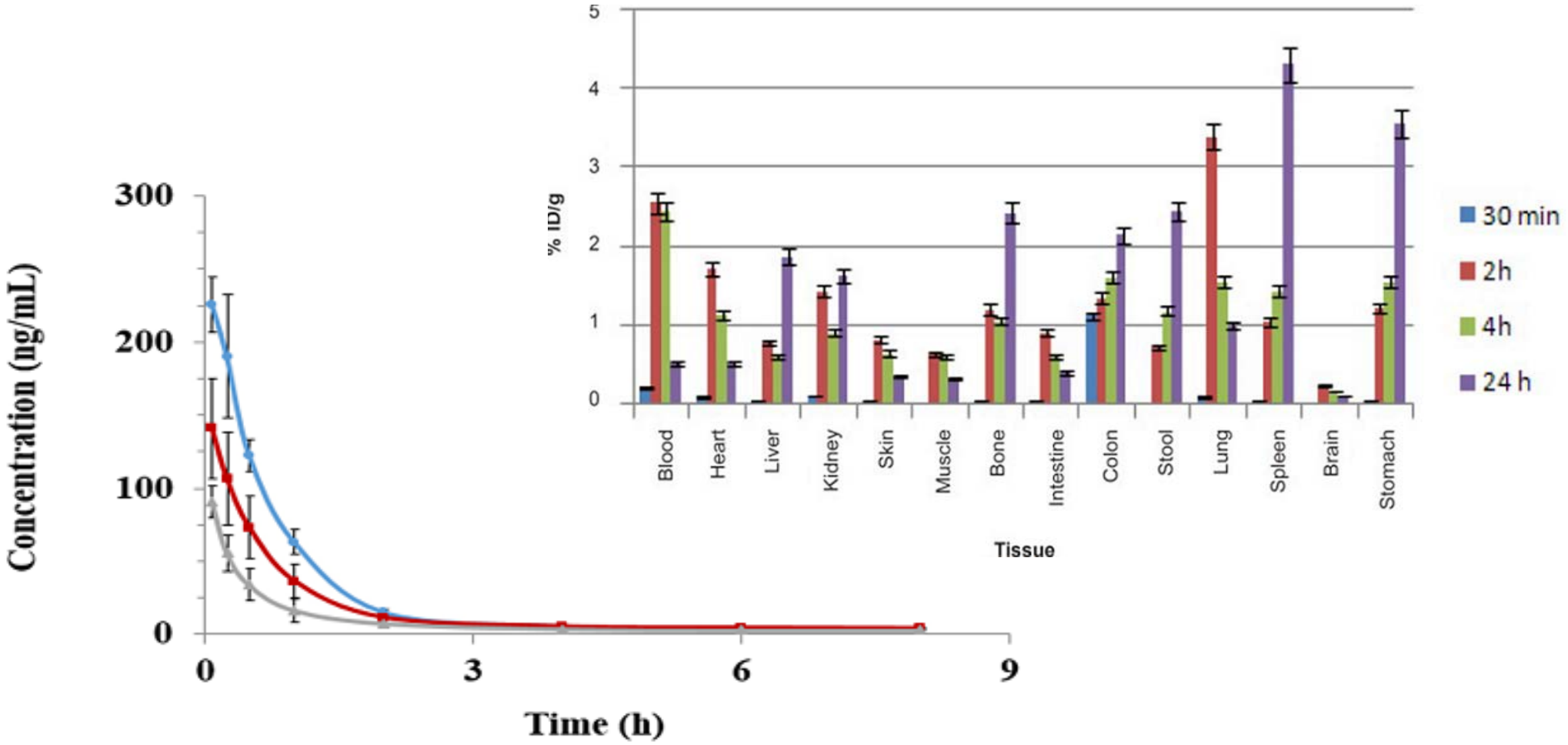


临床前研究（Preclinical Testing）

- 药物筛选；
- 分布及靶向性研究（单抗、ADC、细胞）；
- 药代动力学研究

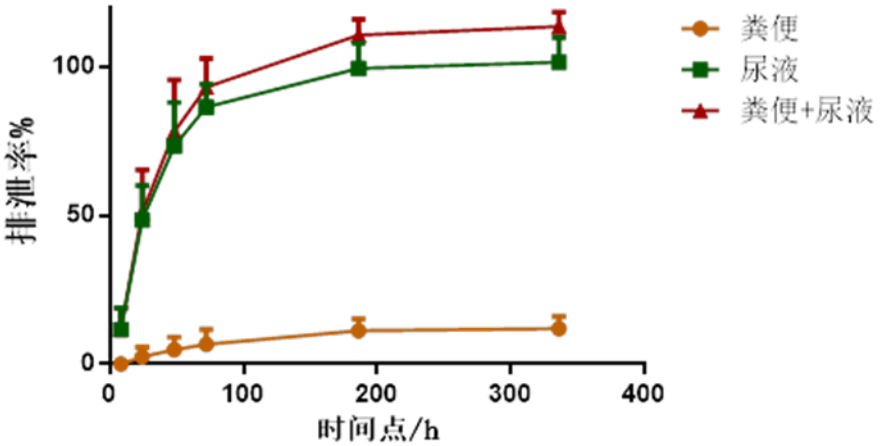
✦传统同位素标记技术应用

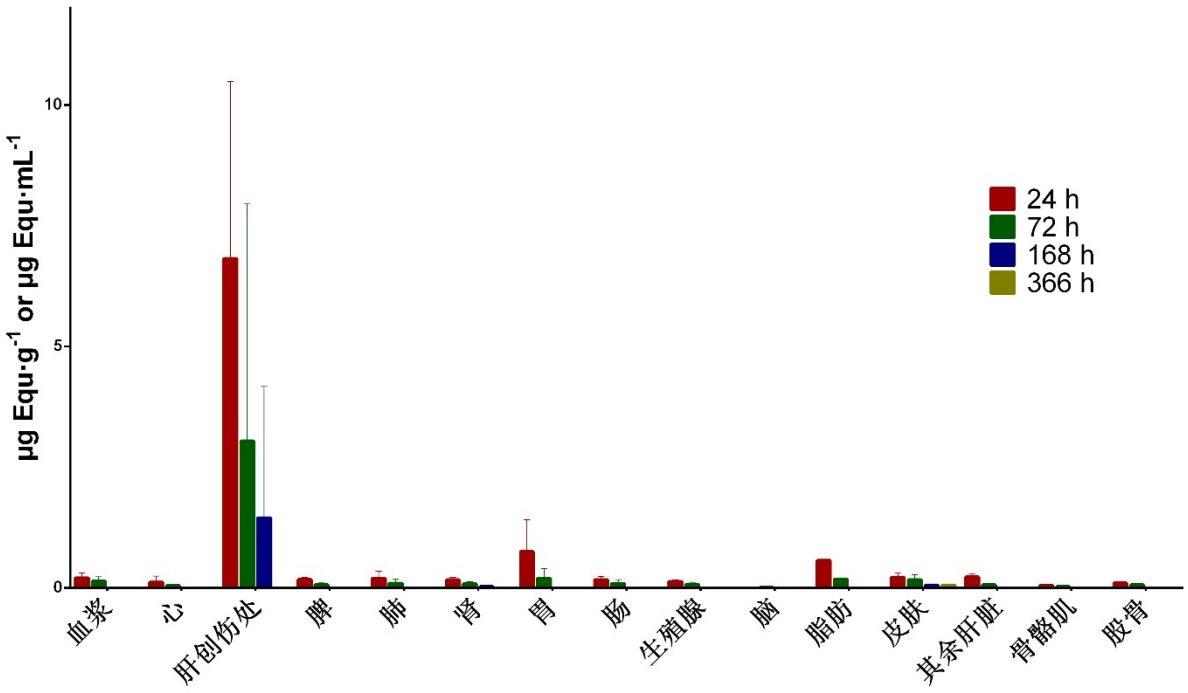
^{125}I标记蛋白药物药代和组织分布研究-离体方法（经典）

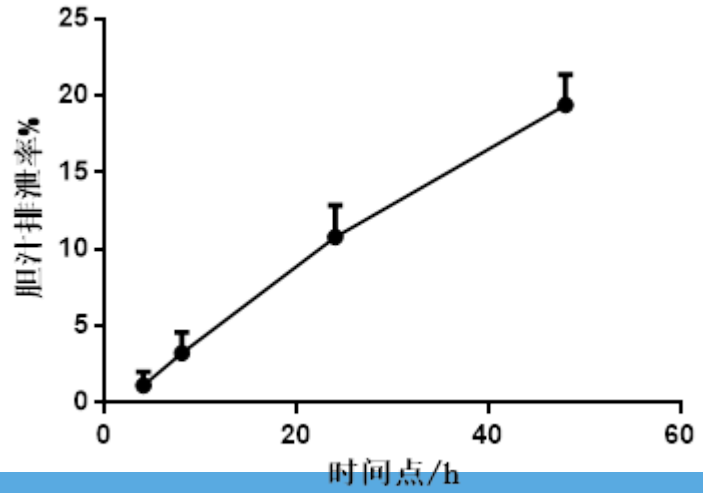


✦传统同位素标记技术应用

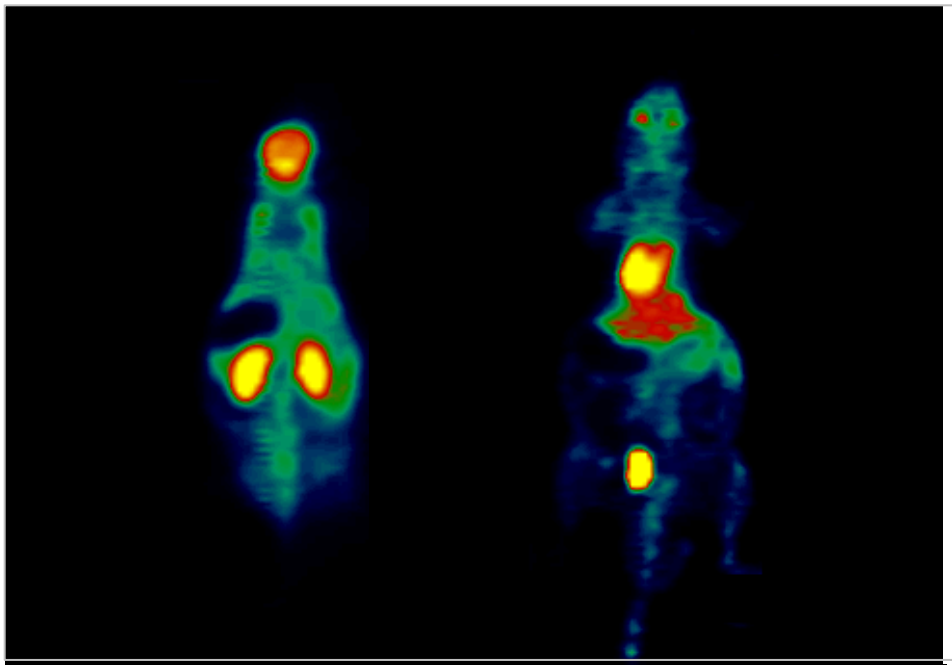
^{125}I-医疗器械组织分布和排泄研究

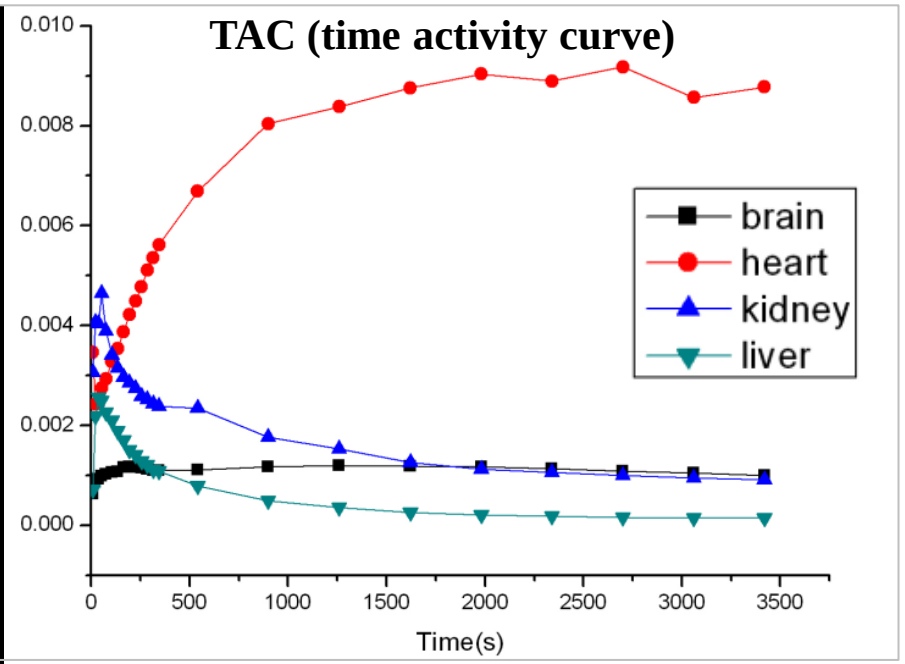






✦ Pharmacokinetics （药代动力学）-分子影像





Time (s)	average	SD	Max	Min
5	0.00012521	0.00009666	0.00042608	0.00001613
15	0.00148731	0.00049741	0.00232502	0.00065094
25	0.00284985	0.00070475	0.00386522	0.00156050
35	0.00365493	0.00078566	0.00532183	0.00229089
…				
3180	0.00073548	0.00026720	0.00135317	0.00042075
…				

动态定量

免杀动物

客观真实

Topics

- 临床前研究（Preclinical Testing）
- 临床研究（Clinical Study）
  - --临床0期研究（Phase 0）
  - --精准医疗（Precision Medicine）
- 平台概览（Platform Overview）

FDA如何定位分子影像

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

- human micro dosing (human Phase 0 studies)
- reduce the failure rate due to suboptimal PK significantly
- used for early internal decision making effectively

- conducted early in phase 1
- limited exposure (single dose administration of <1/100th of the dose calculated to yield a pharmacological effect (≤ 100 µg)
- no therapeutic or diagnostic intent
- aimed at exploring PK in humans

EMEA Position paper (2004)

FDA Guidance: Exploratory IND Studies (2006)

U.S. Food and Drug Administration

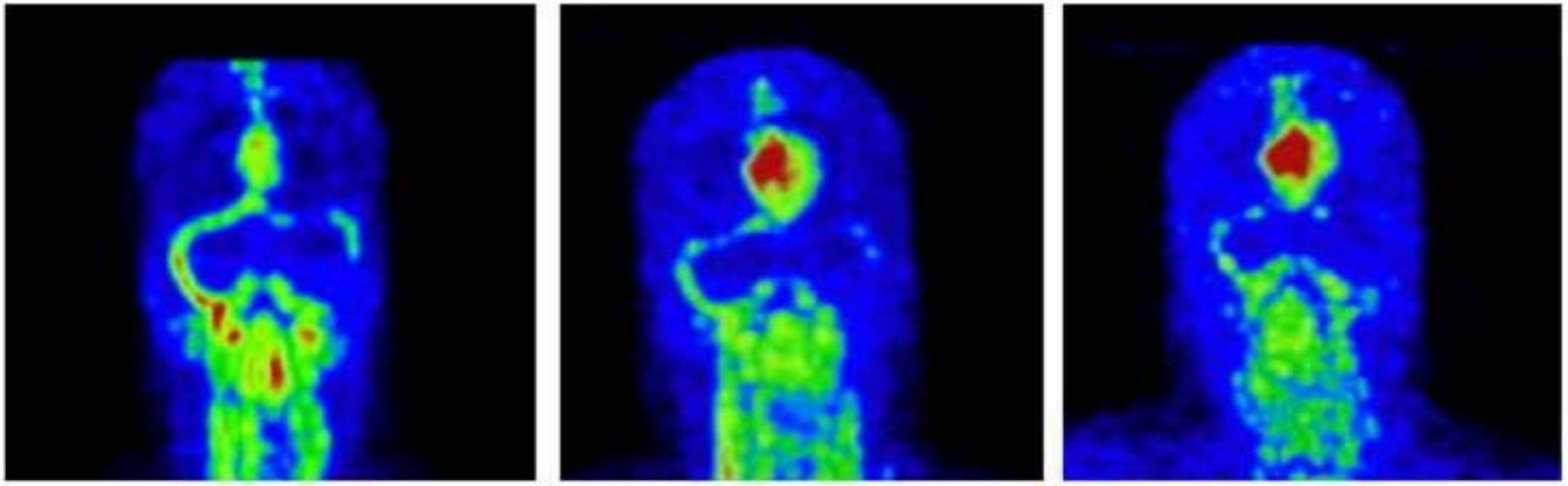
21 CFR PART 361
NO 2004N-0432 微剂量

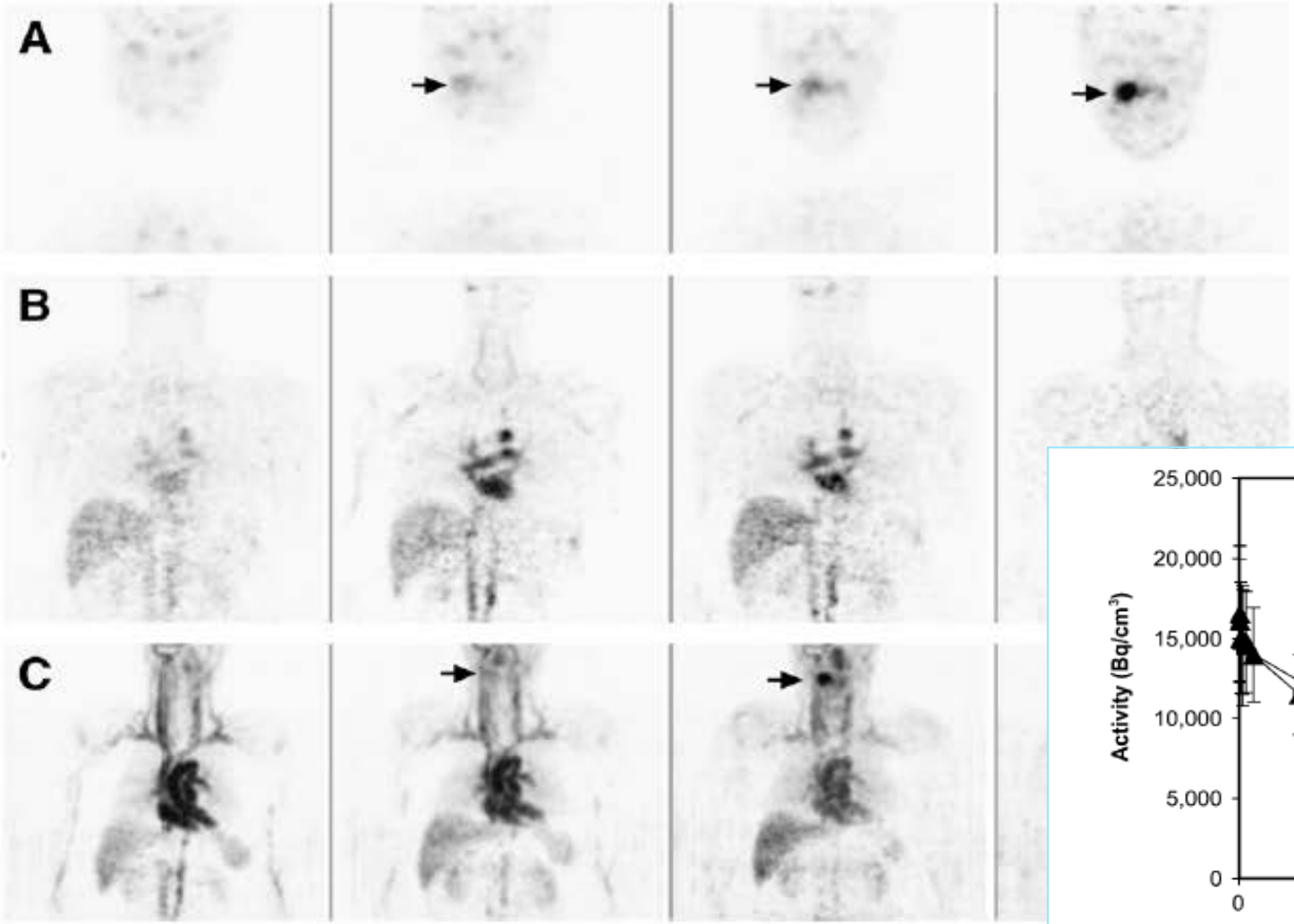
人体微剂量Phase0研究
明显的降低由于PK导致的药物失败率
有效的用于药物早期筛选

Phase0研究

- 微剂量
- 单剂量＜治疗剂量的1/100
- 绝对量≤100ug
- 人体PK、组织分布、靶向性

国内首个^{89}Zr-Antibody Phase 0 研究- (恶性脑胶质瘤)





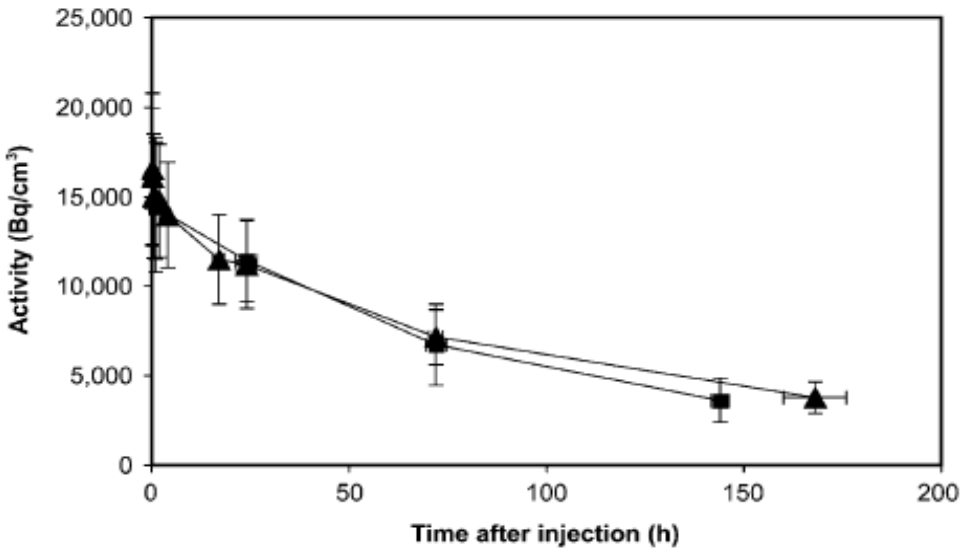


FIGURE 4. Mean ^{89}Zr-cmAb U36 activity in blood (Bq/cm^3) of study population: PET-assessed blood-pool activity within left ventricle of heart (■) and sampled blood-pool activity (▲).

Börjesson PK, et al, J Nucl Med. 2009, 50, 1828-1836.

Topics

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- 临床研究（Clinical Study）

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Personalized Medicine ——个体化医疗

◆ 美国：

2015年奥巴马宣布了新的项目即精准医疗计划在2016财年向该计划投入2.15亿美元推动个性化医疗的发展

◆ 中国：

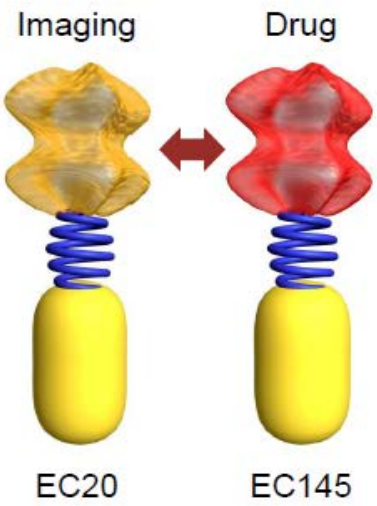
2016年设立国家精准医疗计划

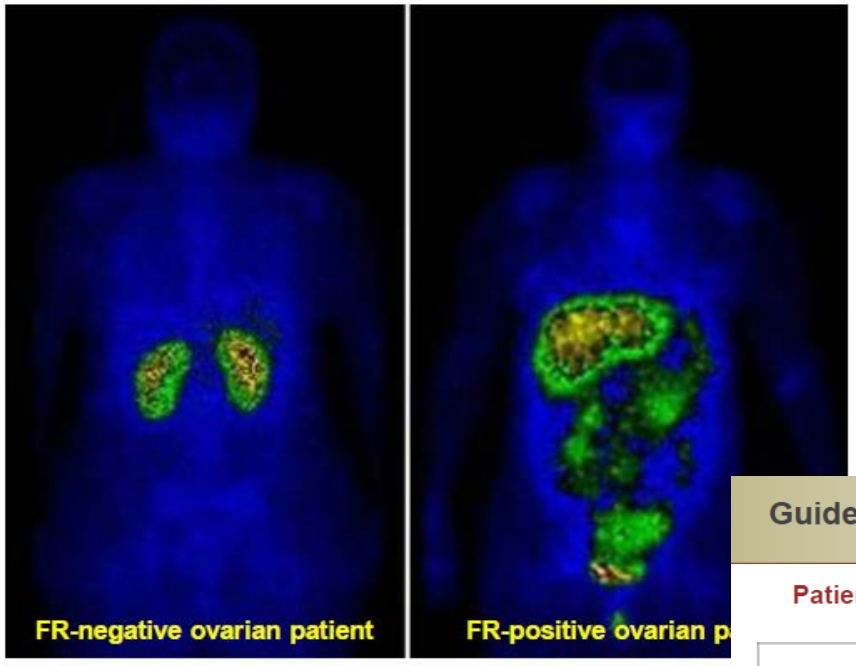
分子影像为精准医疗三大技术之一

2030年前投入600亿

Personalized medicine with guided diagnostics

First full-body, non-invasive, real-time companion diagnostic.



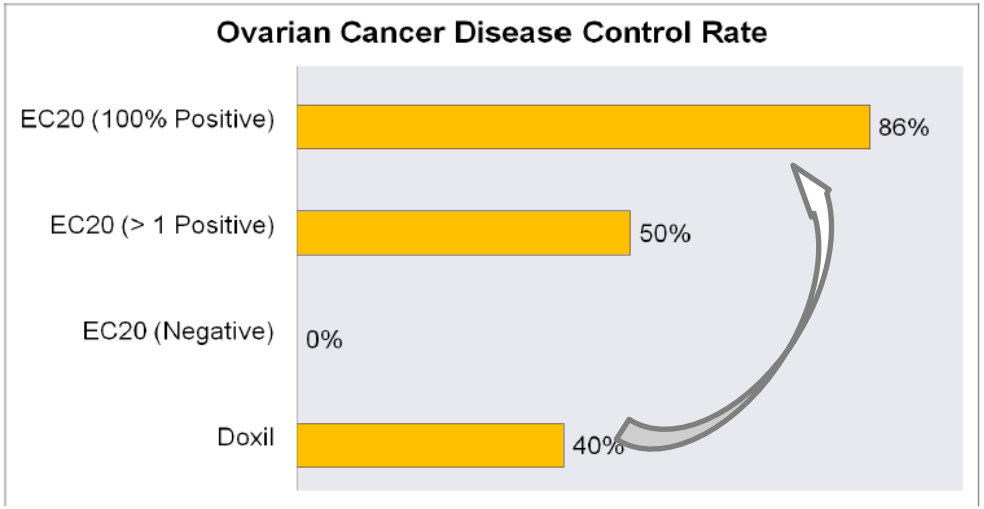


Tc99m-EC20 planar images of ovarian cancer patients 1-2 hours after

CONFIDENTIAL

Guided diagnostics predict response to therapeutic

Patients with 100% of lesions having positive uptake of guided diagnostic (EC20) have 86% disease control rate.

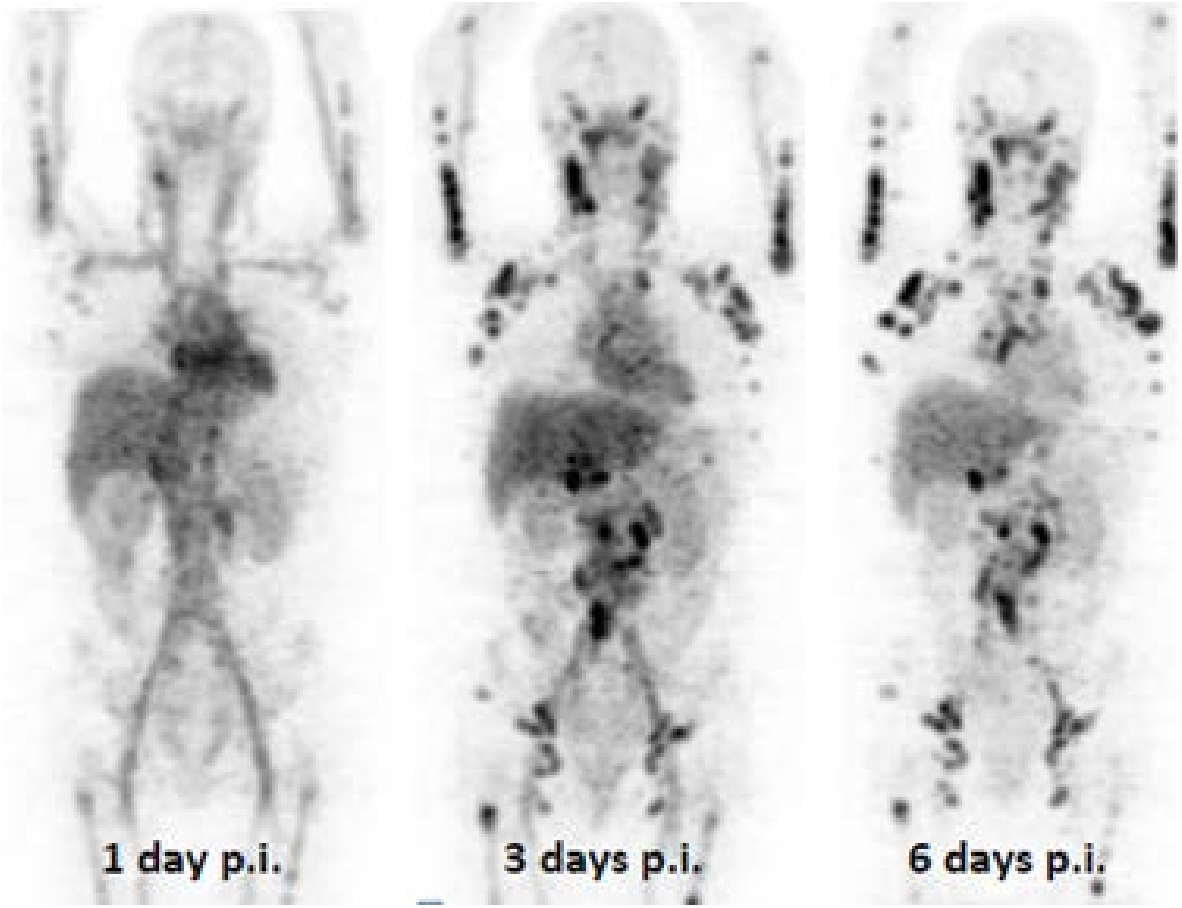


See and treat → Theranostics

Theranostics

利妥昔单抗/美罗华（Rituximab）

89Zr-Rituximab PET imaging　Targeting: CD20

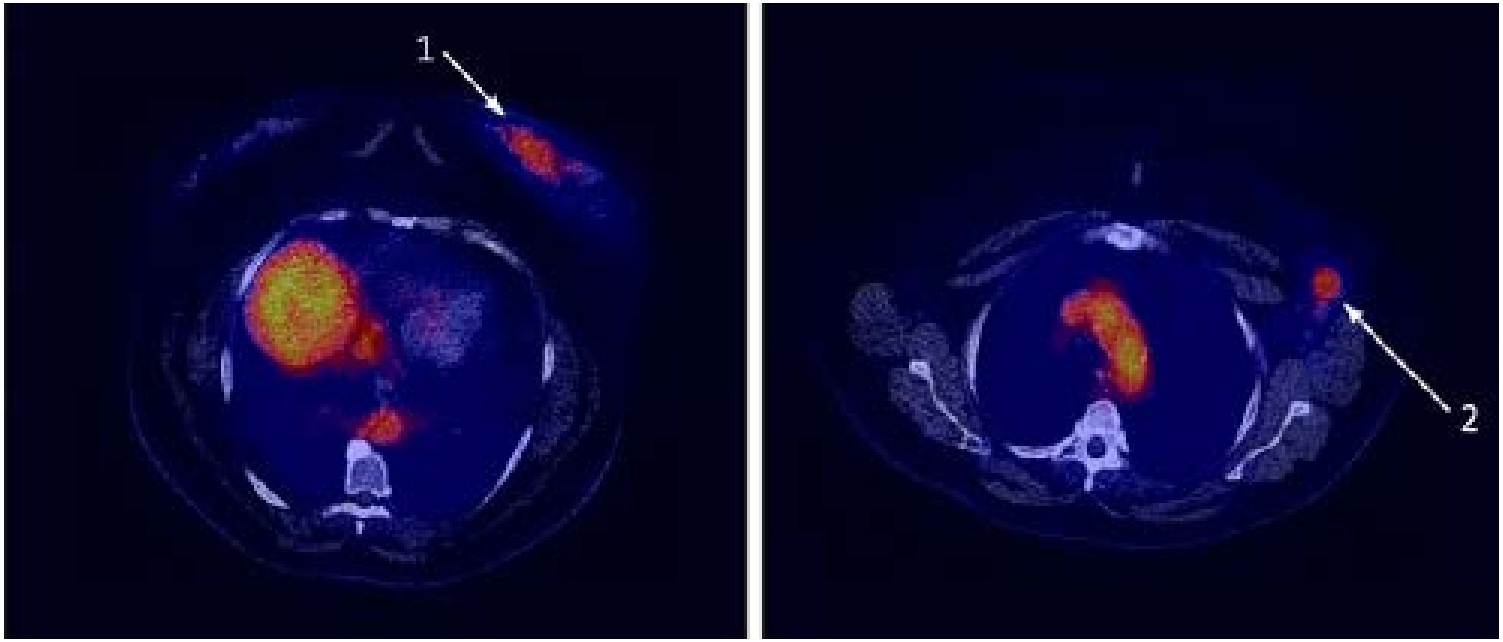


Kristoff Muylle, Patrick Flamen, Bordet Institute, Brussels

贝伐单抗/阿瓦斯汀（Bevacizumab/Avastin）

89Zr-Bevacizumab PET imaging

Targeting: VEGF



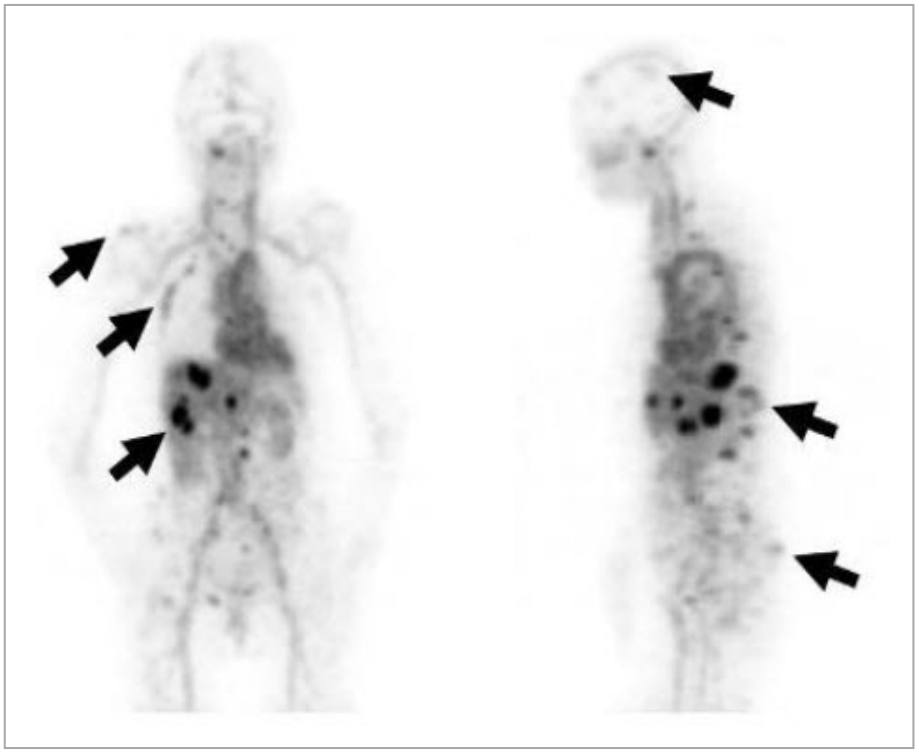
Axial slices of 89Zr-bevacizumab PET from patient with primary breast tumor (1) and lymph node metastasis (2).

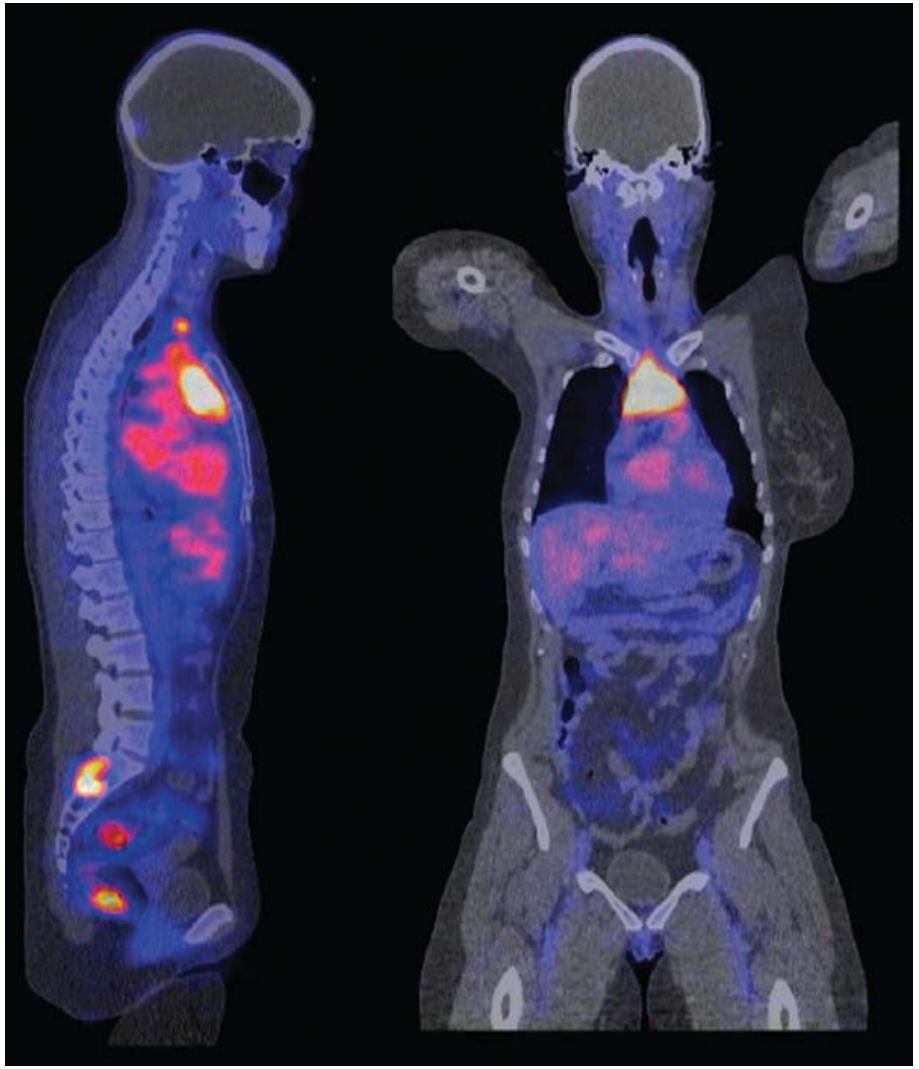
Sietske B.M. Gaykema, Adrienne H. Brouwers, Marjolijn N. Lub-de Hooge,et al.

曲妥珠单抗/赫赛汀（Trastuzumab/Herceptin）

89Zr-trastuzumab PET imaging

Targeting: Her2



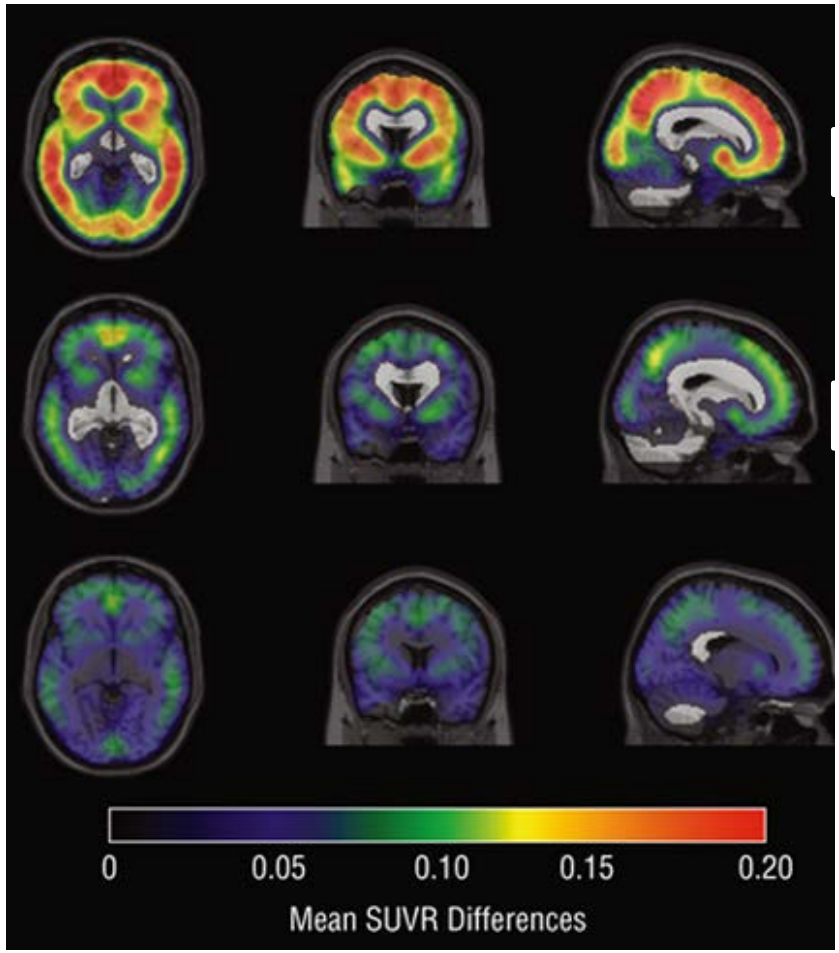


Sietske B.M. Gaykema et al, Journal of Clinical Oncology, Vol 30, No 6

伴随药：诊断药^{18}F-AV45-PET + 治疗药solanezumab (进入临床Ⅲ期)

^{18}F-AV45

老年痴呆(AD)诊断试剂



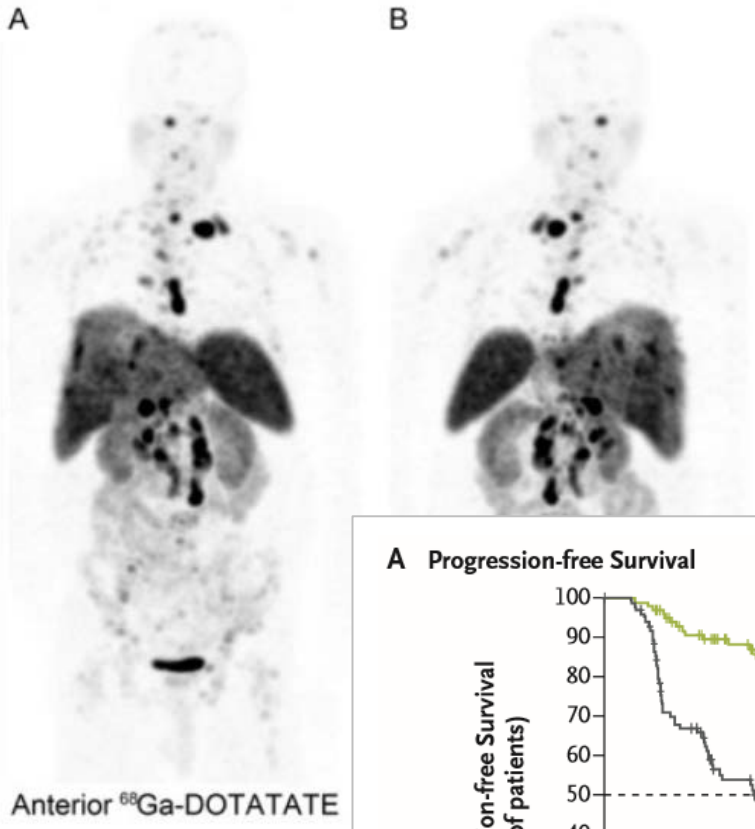
重度AD

轻度AD

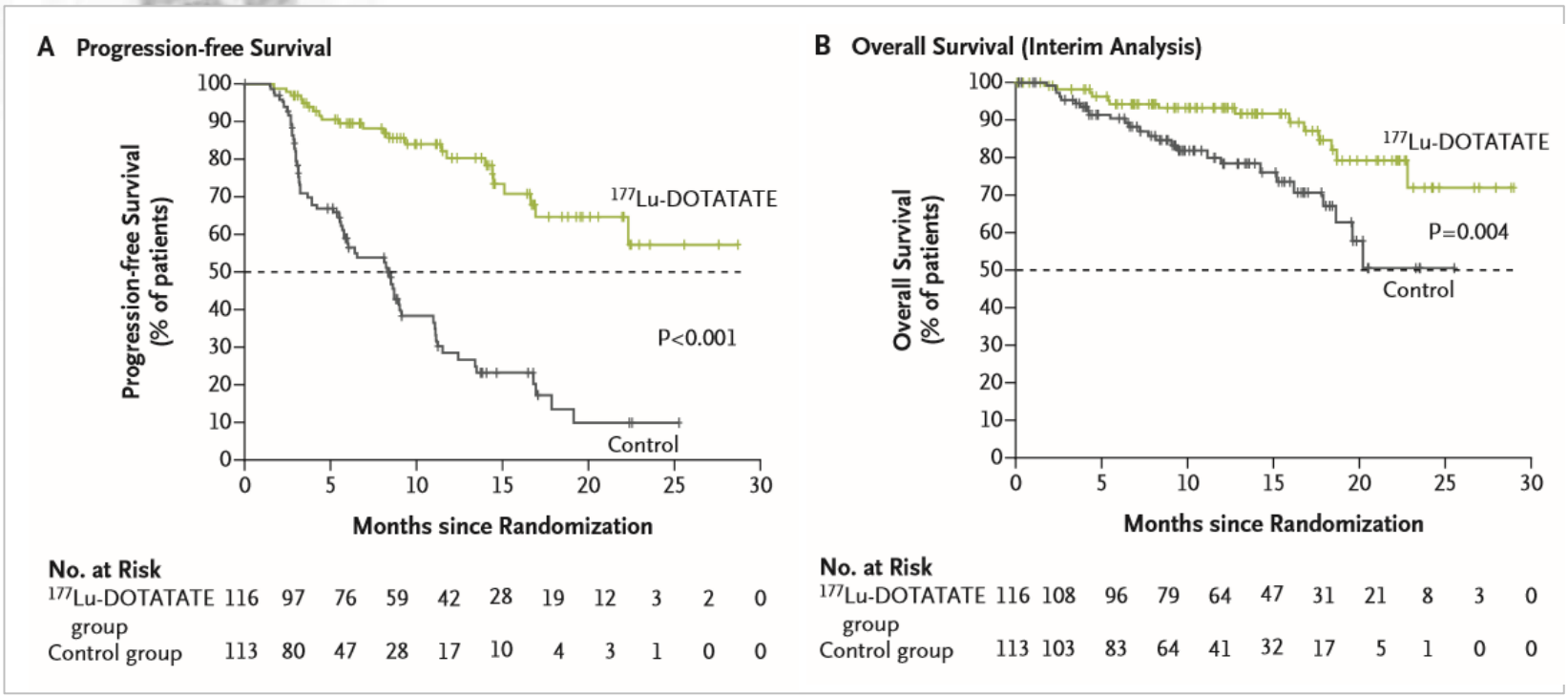
正常老人

2

^{68}Ga- DOTATATE Imaging



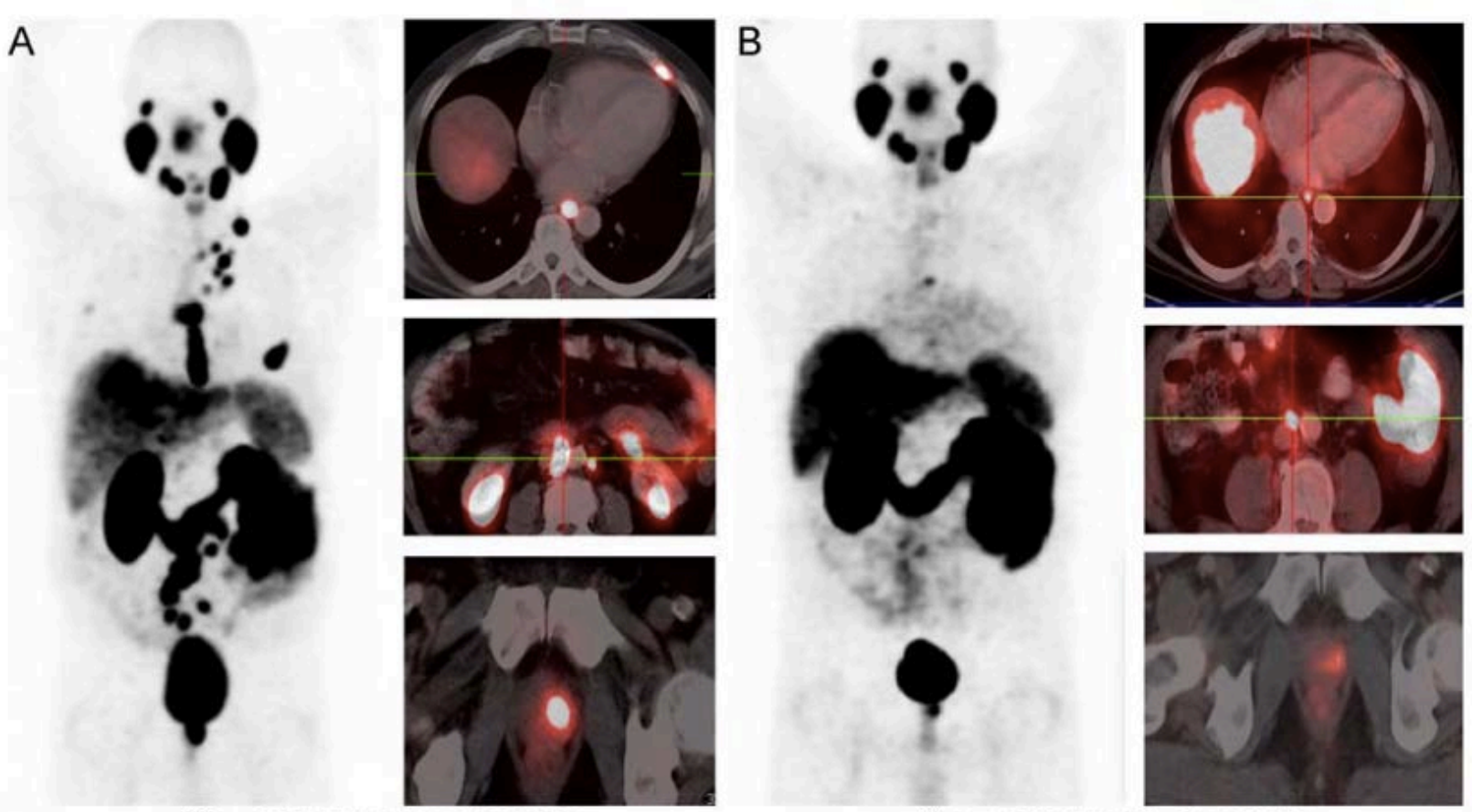
Phase 3 Trial of 177Lu-Dotatate



n engl j med 376;2 nejm.org
January 12, 2017

核素精准治疗案例

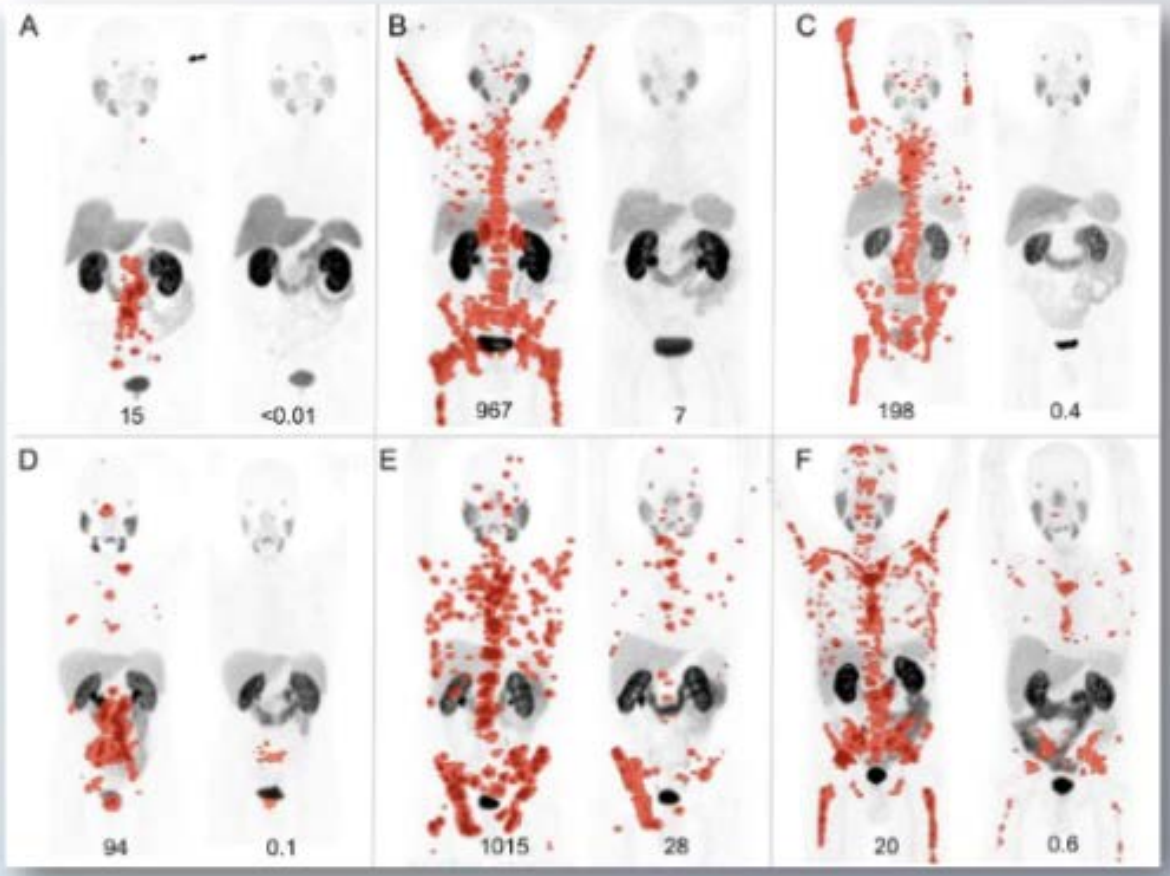
1 ^{68}Ga- and ^{177}Lu-labeled PSMA 2015年SNMMI Image of Year



Martina Weineisen, Journal of Nuclear Medicine, published on June 18, 2015

3

β-particle therapy: Sydney Morning Herald (May 8, 2018)



Courtesy: Jonathan Simons, PCF

https://www.smh.com.au/national/from-lucas-heights-to-petermac-new-prostate-therapy-is-a-game-changer-20180508-p4ze1f.html

JOHNS HOPKINS MEDICINE

Reduced cancer activity observed in six men involved in Peter Mac's trial. Red dots indicates sites of prostate cancer before (left side) and after (right side) treatment with LuPSMA.

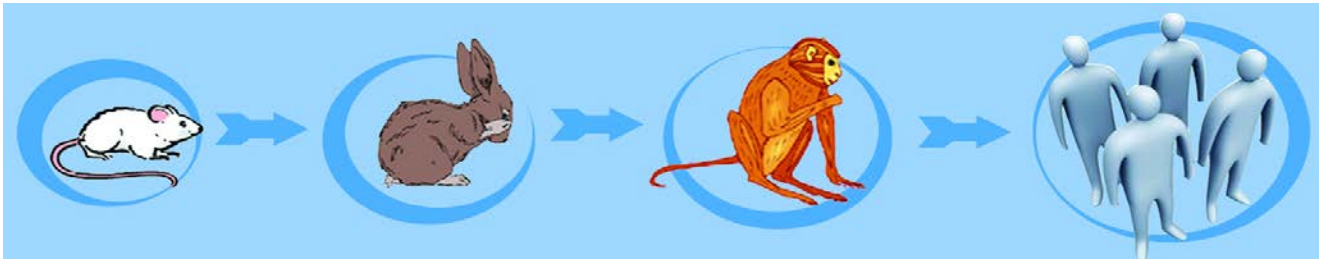
Photo: Peter MacCallum Cancer Centre

Topics

- 临床前研究（Preclinical Testing）
- 临床研究（Clinical Study）
  - --临床0期研究（Phase 0）
  - --个体化医疗（Personalized Medicine）
- **平台概览（Platform Overview）**

MITRO（米度） -- *Molecular Imaging Translational Research Organization*

2010年8月开拓分子影像业务于无锡，2012年11月成立南京米度，国内首家放射性药物及分子影像专业CRO公司，具备FDA/CFDA双申报经验。



关键技术一：放化标记（Radiolabeling）

小分子

^{18}F、^{11}C

常规示踪剂：33
客户定制合成：20

大分子

^{18}F、^{125}I、^{89}Zr、^{131}I

生物蛋白及结构修饰蛋白：29
抗体/抗体片段及ADC：53
高分子及纳米材料：10

肽类

^{18}F、^{68}Ga、^{188}Re、^{99m}Tc

小分子肽：10

核酸类

^{89}Zr、^{131}I、^{32}P

DNA/RNA：3

中药类

^{125}I

多糖：1

细胞类

^{89}Zr

干细胞/CAR-T细胞：3
中性粒细胞：1
肿瘤细胞：3
细菌/真菌：2

医疗器械

^{125}I

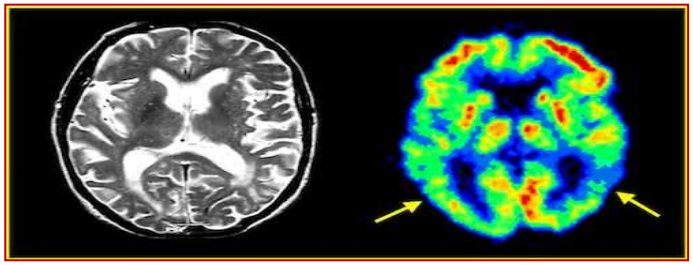
氧化纤维素类：4
脱细胞真皮基质类：1
胶原蛋白交联材料：2

已标记化合物
170余种

关键技术二：影像分析技术

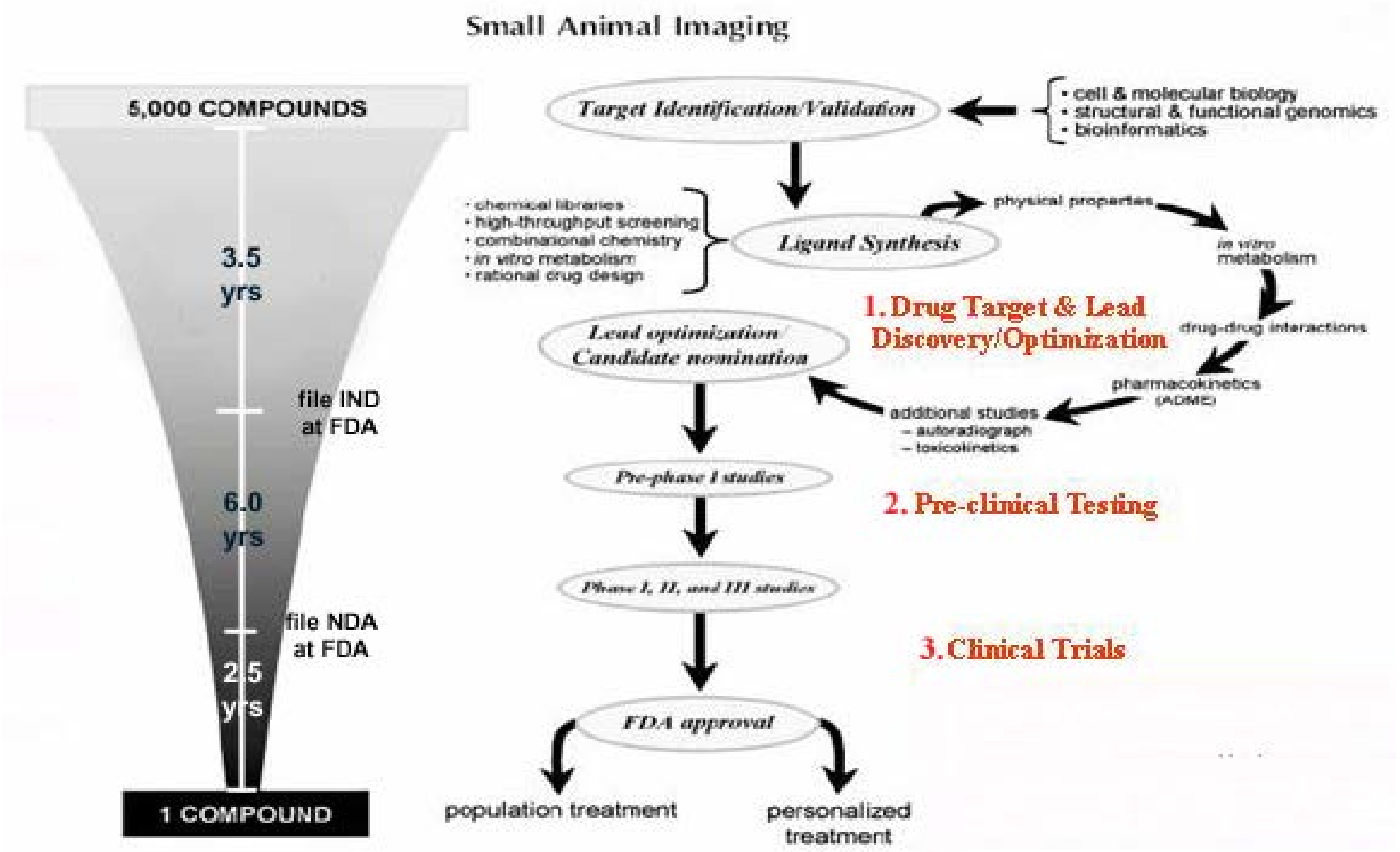
π.pmod

开发的PET图像分析工具



PKIN	药代动力学通用分析工具
PXMOD	药代动力学像素级分析工具
PBAS	图像处理和感兴趣区域分析工具
PFUS	图像配准与合并工具
PSEG	PET图像分割工具
P3D	三维立体图像重建工具
PCARDP	PET心脏图像分析工具
PCARDM	MR心脏图像分析工具
PALZ	FDG PET阿尔茨海默病分析工具
PNEURO	PET脑图像分析工具
PGEM	几何模型和仿真接口工具

Molecular Imaging in Drug Development



From S.C. Van Cauter, BioScan

“给分子装上GPS，做微观世界的导航者”

谢谢！