放射性药物研发与应用

成都纽瑞特医疗科技有限公司

Chengdu New Radiomedicine Technology CO. LTD.

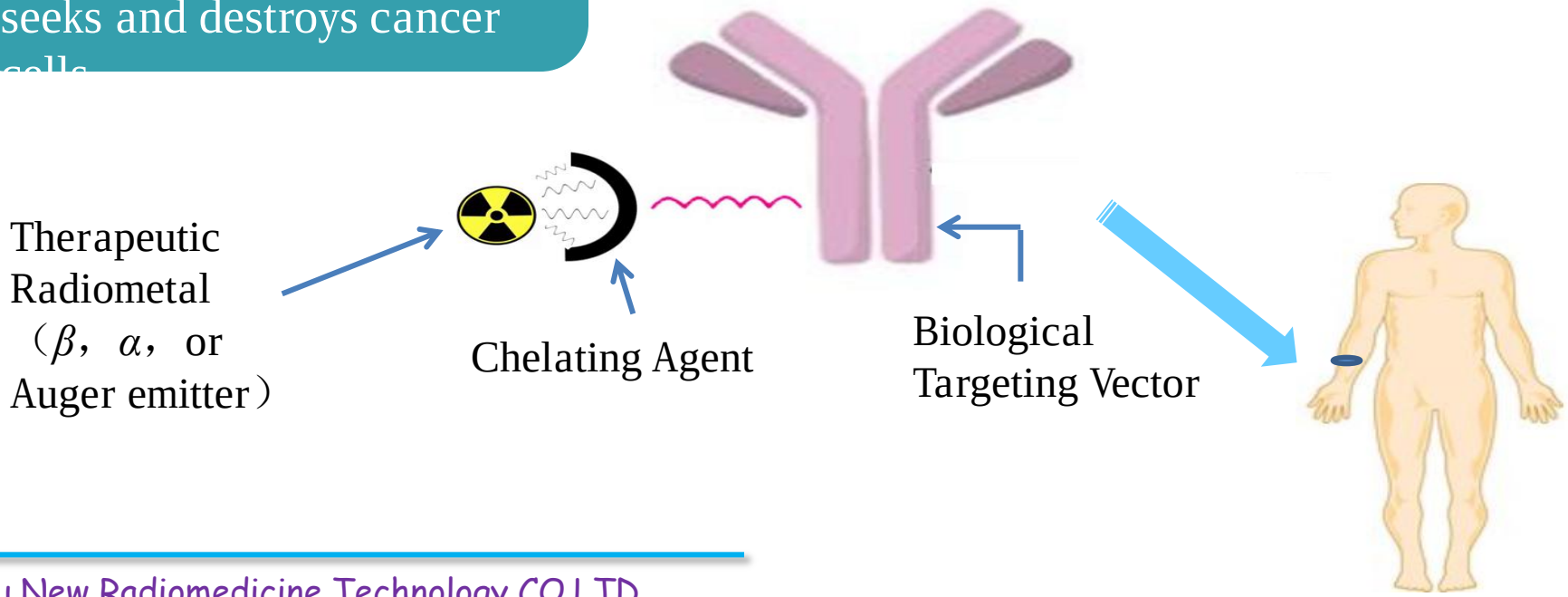
马欢

2018年7月1日

What is Radioisotope Therapy?

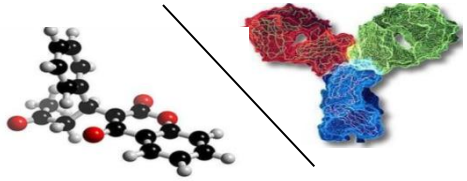
Precision treatment in which a radioactive drug compound seeks and destroys cancer cells

Radio - Pharmaceutical

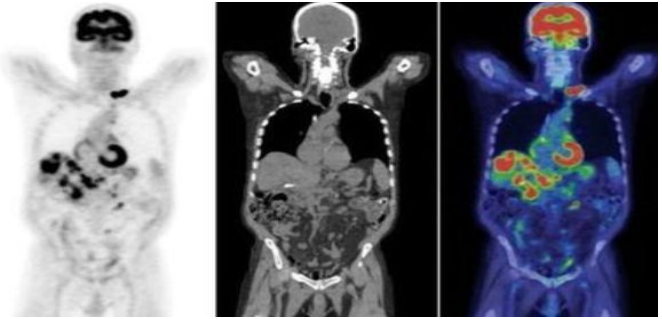


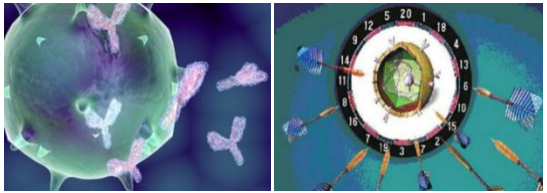
- ✓ Highly selective—kills cancer cells and spares healthy cells
- ✓ Can be tailored to the unique biologic characteristics of the patient and the molecular properties of the tumor
- ✓ Virtually all performed as outpatient procedures
- ✓ Side effect rates less than other treatments

Benefits of Radioisotope Therapy

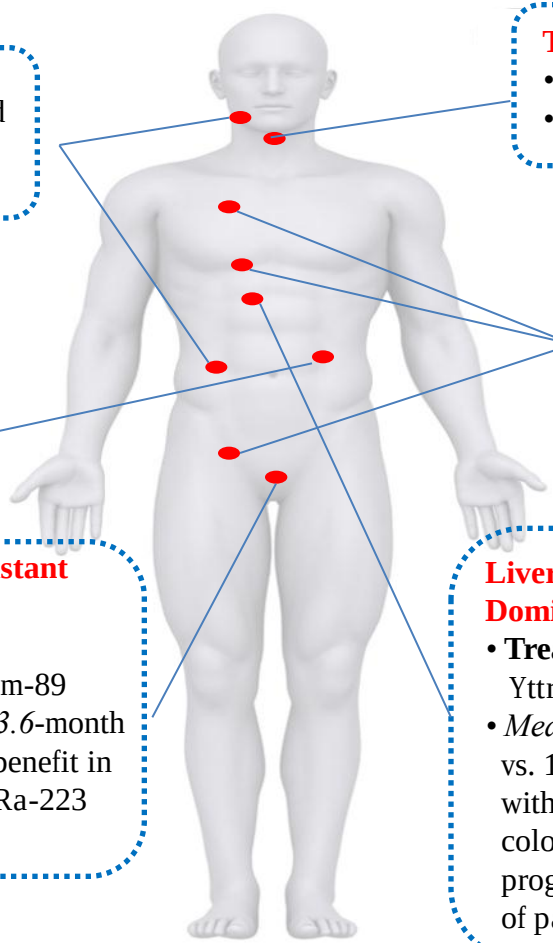


Radio - Pharmaceutical





Targeted Cancer Treatment with Nuclear Medicine Therapy



Non-Hodgkin's Lymphoma

- **Treatment:** yttrium-90 labeled ibritumomab tiuxetan
- *Effective in 75% of patients*

Thyroid Cancer

- **Treatment:** sodium iodide iodine-131
- *Cure rates in excess of 90%*

Neuroblastoma

- **Treatment:** iodine-131 metaiodobenzylguanidine (MIBG)
- *Overall survival rate of 69%*

Metastatic Neuroendocrine Tumors

- **Treatments:** lutetium-177 or yttrium-90 labeled Somatostatin analogue peptides
- *Overall response rates exceeding 30%* in heavily pretreated patients

Bone Metastases from Castration-Resistant Prostate Cancer

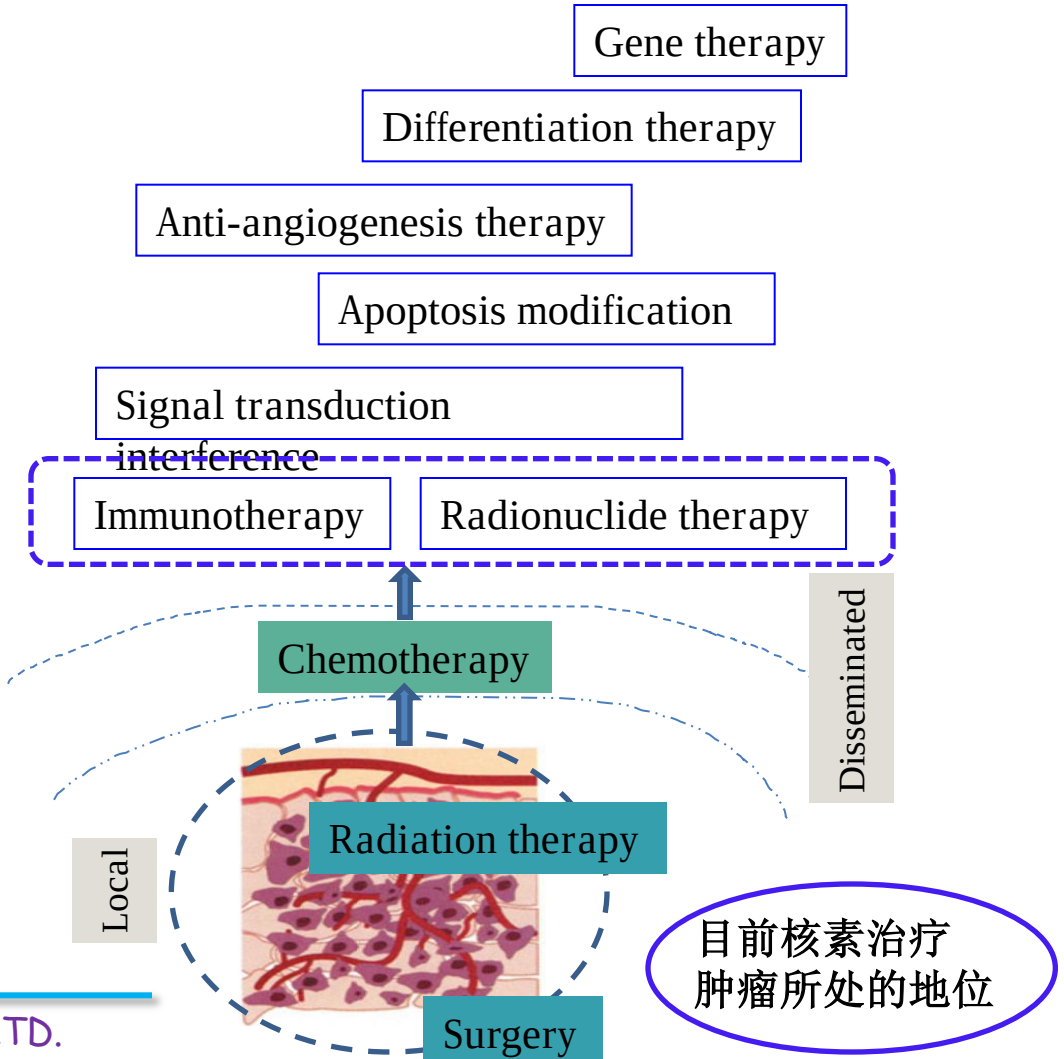
- **Treatments:** radium-223 dichloride, samarium-153 lexidronam, and strontium-89
- *Nearly comparable adverse events and 3.6*-month overall survival benefit and 5.6-month benefit in time to first skeletal-related event with Ra-223 dichloride compared to placebo

Liver Cancer (Hepatocellular Carcinoma) and Liver-Dominant Metastatic Disease

- **Treatment:** Selective internal radiation therapy (SIRT) with Yttrium-90 microspheres
- *Median survival rate for liver cancer patients of 20.5 months* vs. 17.4 months with SIRT as compared to chemoembolism, with less toxicity. In liver-dominant metastatic disease from colon cancer, partial response, stable disease, and progressive disease seen in 10.2, 60, and 30 percent of patients, respectively.

放射性核素治疗进展

- ^{90}Y、^{177}Lu等金属核素标记抗体、多肽，解决了脱标及定位标记问题
- 诊疗一体化，$^{68}Ga/^{90}Y$，$^{123}I/^{131}I$等，解决或优化了患者筛选及吸收剂量评估
- 小分子载体研究活跃（一次通过摄取率↑、穿透性↑）
- 实体瘤的疗效获得明显进展—NET、前列腺癌
- ^{223}Ra开启了核素治疗的α射线治疗时代



Organic tissue

Alpha Particles

Stopped by a sheet of paper

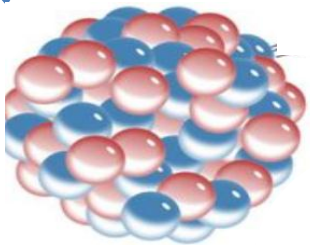
Beta Particles

Stopped by a layer of clothing or by a few millimeters of substance such as aluminium

Gama Particles

Stopped by a several feet of concrete or a few inches of lead

Radiation Source



γ-emitters (100—400keV) for SPECT

^{99m}Tc, ^{123}I, ^{201}Tl

used all over the world for now-routine clinical procedures

β^+ emitters for PET

^{18}F, ^{68}Ga, ^{82}Sr, ^{11}C, ^{13}N, ^{15}C

A useful diversity of half-lives chemistry, and emission characteristics

Targeted Radiotherapy

A rapidly growing field with interest in man β- (^{177}Lu, ^{90}Y, ^{131}I), α- (^{211}At, ^{223}Ra, ^{225}Ac), Auger- (^{111}In, ^{125}I, ^{131}I), and X-ray (^{103}Pd) emitting radionuclides

Theranostics

- The merger of diagnostic information with therapeutic tools
- Use biomakers to determine personalized doses of a treatment

Advantages

- *Decrease "side effects"*
- Increased compliance
- Development time and costs are shared by two drugs
- Increased optimal therapy

Disadvantages

- Must identify and characterize biomakers
- Complexity in developing the ligand
- Physician hesitancy
- Regulatory hurdles

Radiochemistry partnered with Nuclear Medicine offers an excellent opportunity for theranostic advances

Theranostic Potentials in Nuclear Medicine

Halogenation-

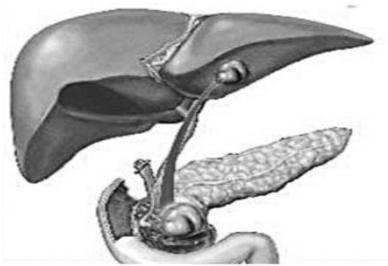
^{123}I or ^{124}I for diagnostic， **^{131}I** for therapy

Metals-

- Matched pair （**^{99m}Tc** for diagnostic， **^{186}Re or ^{188}Re** for therapeutic； **^{68}Ga** for diagnostic，**^{177}Lu or ^{90}Y** for therapeutic）
- Isotopic pairs （**^{86}Y** for diagnostic，**^{90}Y** for therapeutic）
- radionuclides emitting both diagnostic and therapeutic radiations （**^{177}Lu**（β^-，γ）；**^{64}Cu**（β^-，β^+））

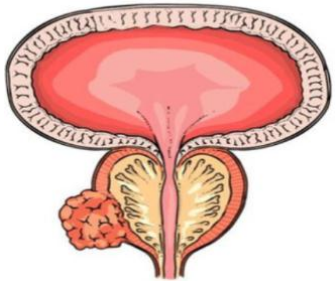
Tumor Theranostic

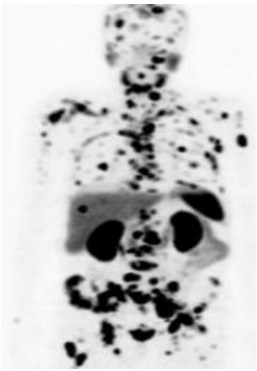
神经内分泌肿瘤



$^{68}Ga/^{177}Lu$-DOTATATE

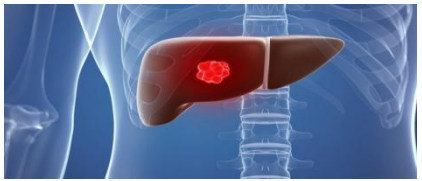
前列腺癌

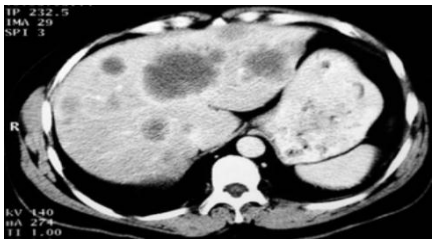




$^{68}Ga/^{177}Lu$-PSMA

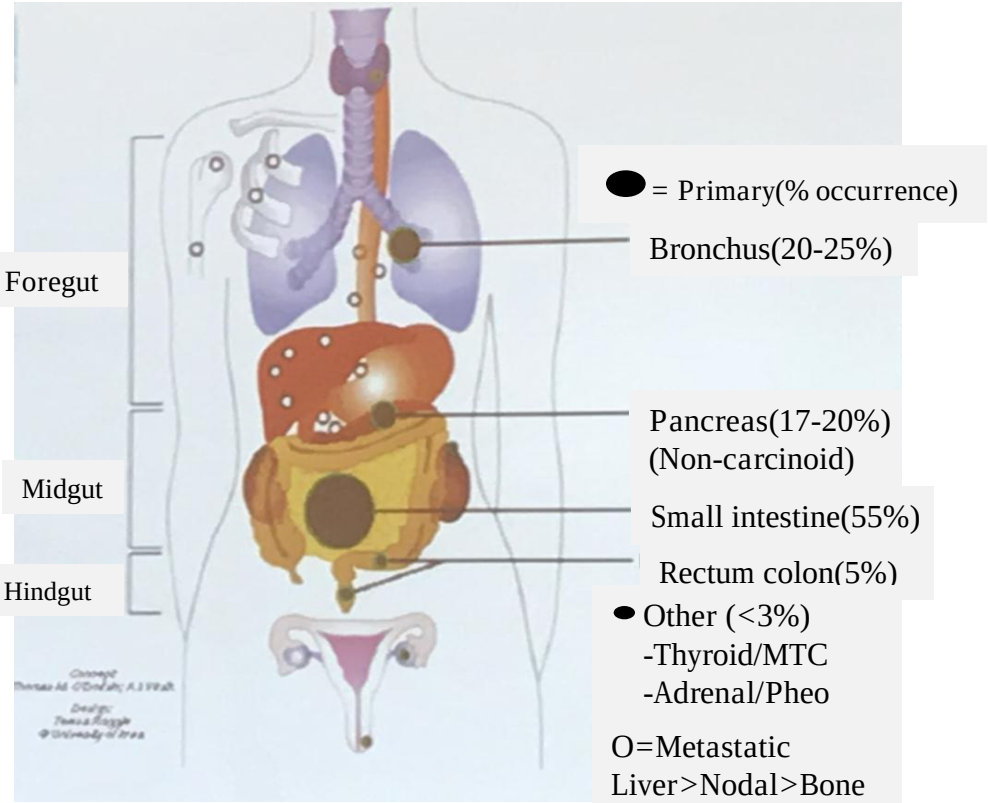
肝细胞癌

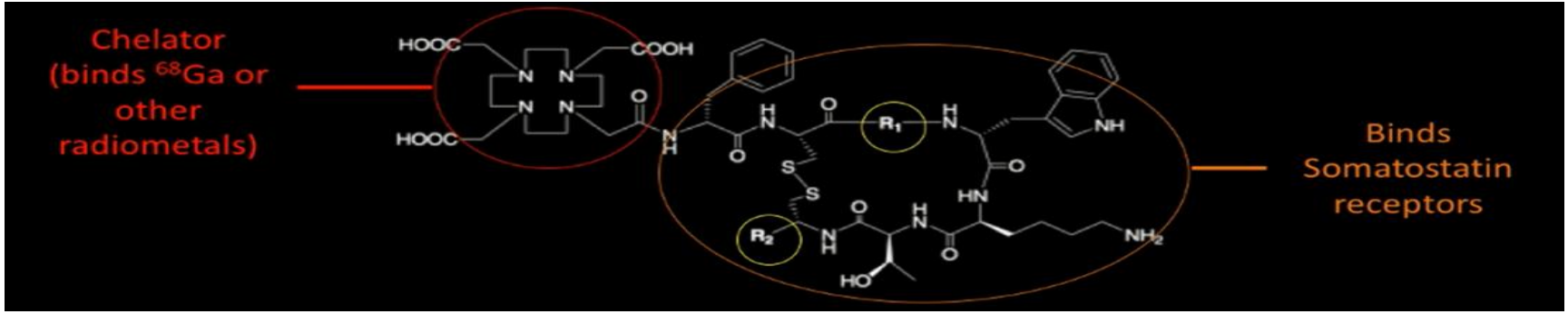




^{90}Y-微球栓塞治疗

Anatomical distribution of neuroendocrine tumors

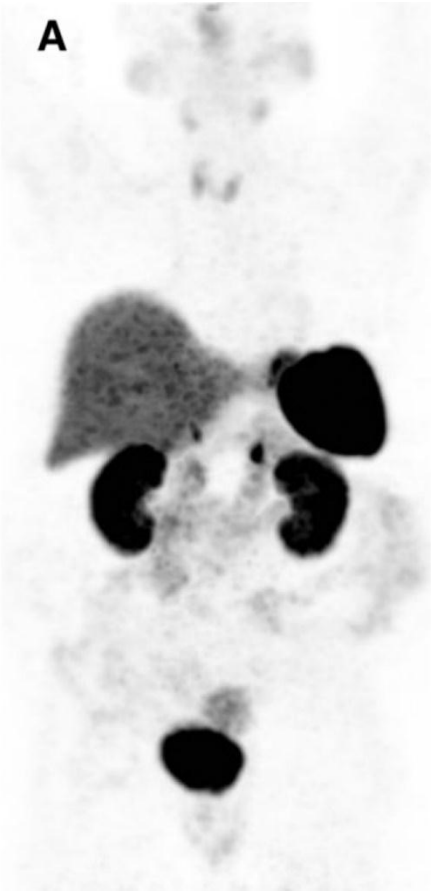




compound	R1	R2
DOTA-OC	Phe	Thr(ol)
DOTA-TOC	Tyr	Tyr(ol)
DOTA-TATE	Tyr	Thr
DOTA-NOC	Nal-1	Thr(ol)
DOTA-NOC-ATE	Nal-1	Thr

SSR binding analogs are based on the octreotide (OC) scaffold
Most commonly used analogs are DOTA-TATE and DOTA-TOC

Antunes et al. Eur. J. Nucl Med. Mol Imag. 2007
Poeppel et al. Recent Res. Cancer Res. 2013

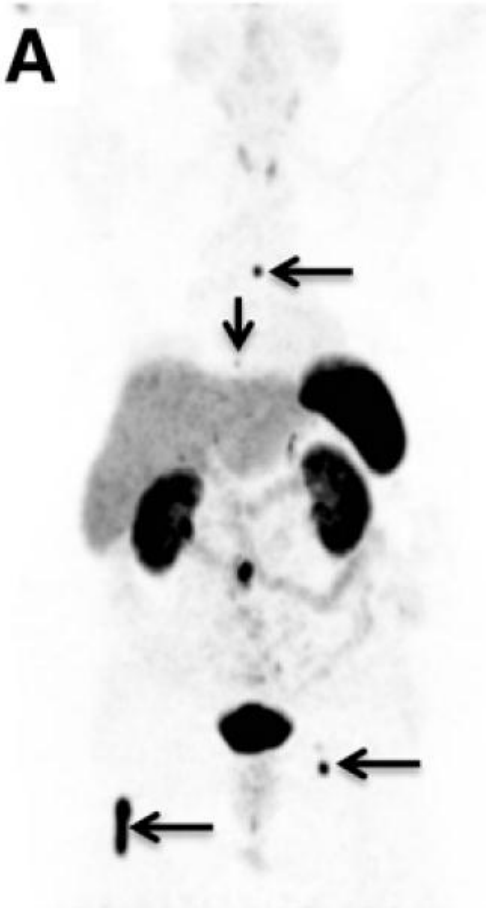


Normal biodistribution of 68Ga-DOTATATE on volumetric (maximum-intensity-projection, MIP) image.

PET/CT images showing physiologic intense uptake in pituitary, liver, spleen, kidneys, adrenals, and uncinate process of pancreas and variable degree of uptake in thyroid, intestine, and urinary bladder

- ✓ Clearance is via urinary and (lesser) hepatobiliary pathways
- ✓ Highest absorbed dose is to adrenals, kidneys, and bladder wall

Lisa Bodei, et al , J. Nucl M , 2017,58(11)



Upstaging of patient with history of small intestine NET and 6.5-cm lesion within right proximal femur with benign appearance at prior MRI.

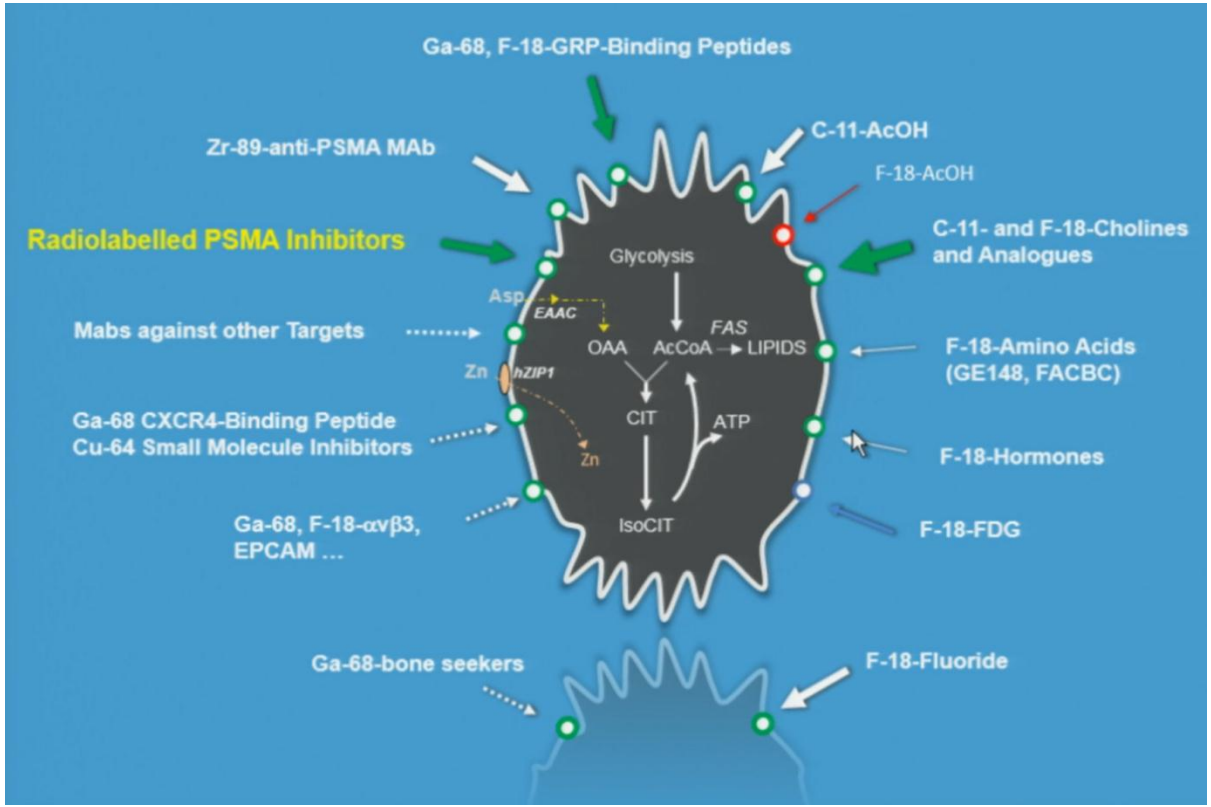
DOTATATE maximum-intensity-projection image revealed multiple mesenteric and pelvic, as well as multiple unexpected osseous, metastases (arrows).

Lisa Bodei, et al , J. Nucl M , 2017,58(11)

Somatostatin receptor scintigraphy (SRS) of patient in our series after the first, second and fourth dose with 177Lu-DOTATATE showing **a reduction in uptake of some lesions** and **the disappearance in some lesions** and being considered as **partial remission** according to the imaging techniques. Thyroglobulin (Tg) decreased along the treatment.

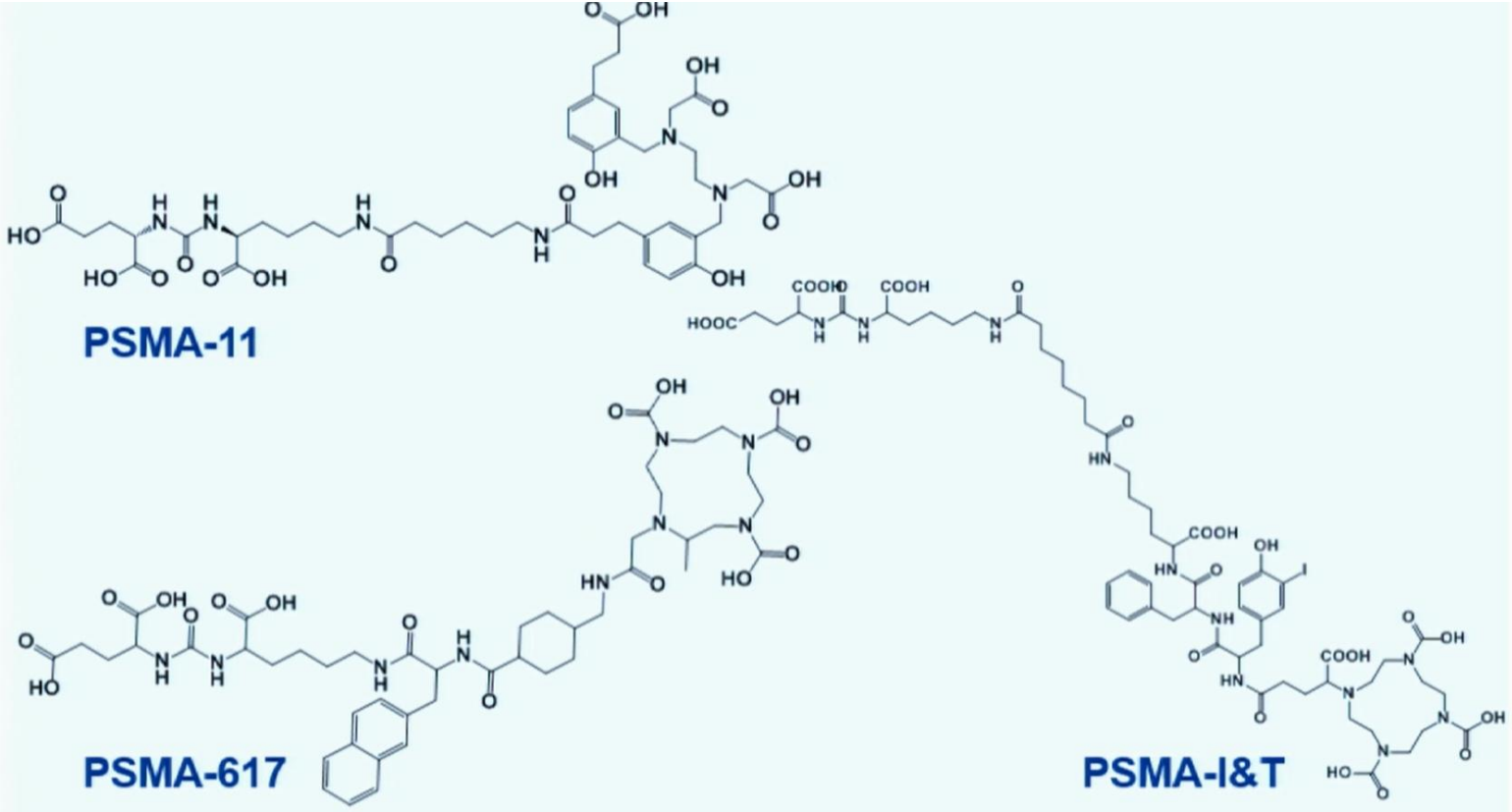
I. Hervás , et al, Rev Esp Med Nucl Imagen Mol.2017;36(2):91–98

Molecular Imaging of Prostate Cancer by PET



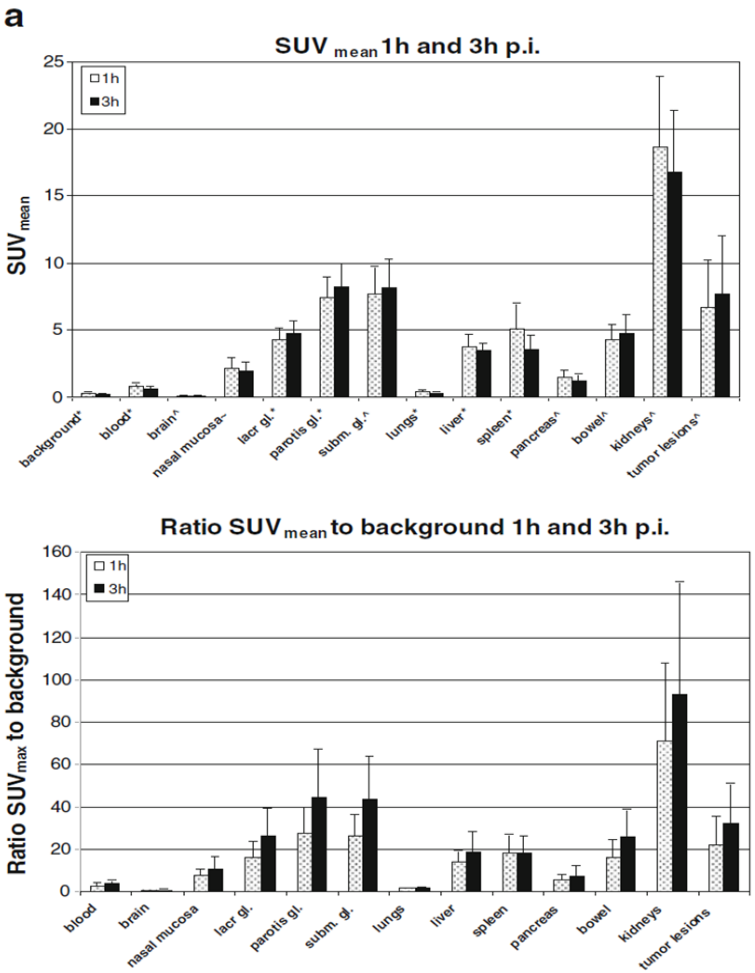
2016 SNMMI Courtesy Hans-Jurgen Wester , TUM

Structure from PSMA Ligands Samples



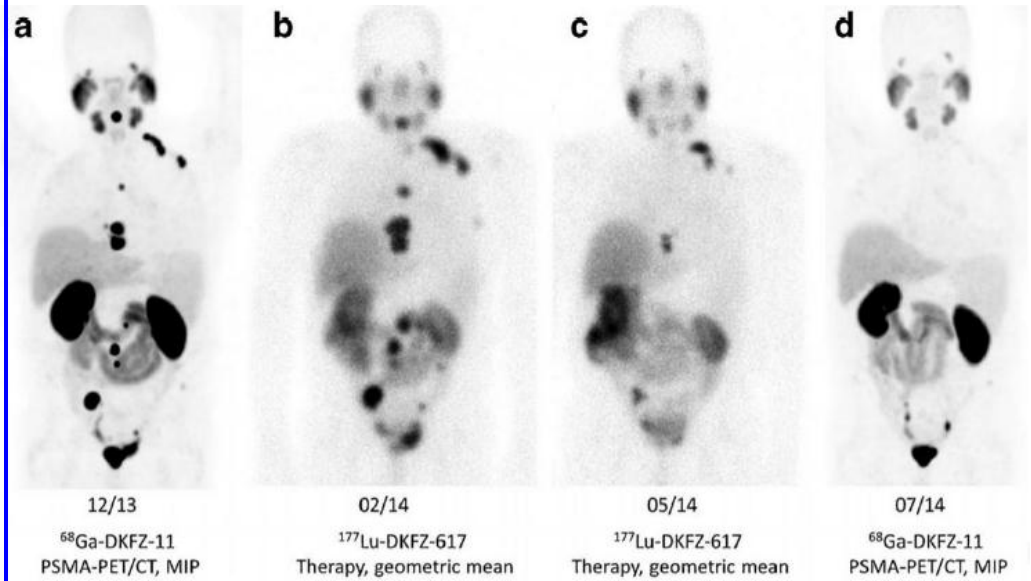
MIP of a patient with normal biodistribution of ^{68}Ga-PSMA

Accumulation is seen in lacrimal and salivary glands, nasal mucosa, liver, spleen, bowel, kidneys and bladder



A. Afshar-Oromieh, et al, Eur J Nucl Med Mol Imaging (2013) 40:486–495

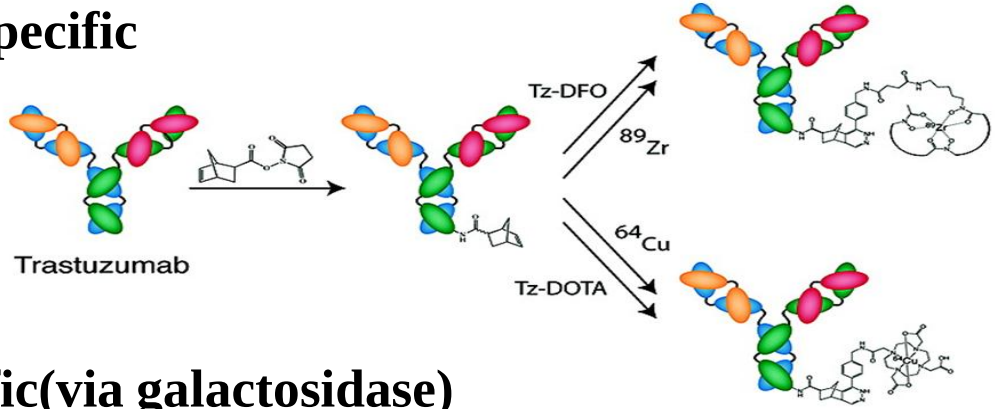
Patient with Gleason prostate cancer. No evidence of metastatic disease on conventional imaging including MRI, bone scintigraphy or CT. Minimal reduction of PSA for 9 to 7 following radical prostatectomy. Post-operative PSMA PET/CT demonstrates osseous metastatic disease that was occult on conventional imaging.

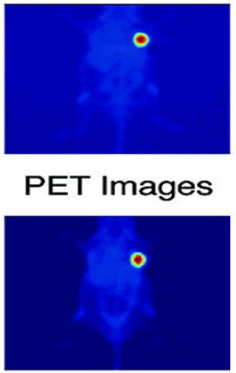


Patient with metastatic prostate cancer and high uptake on ^{68}Ga PSMA PET/CT. The patient was treated with a cumulative activity of 7.4 GBq using ^{177}Lu PSMA. Restaging reveals a striking radiologic response and PSA levels decreased from 38.0 to 4.6 ng/ml.

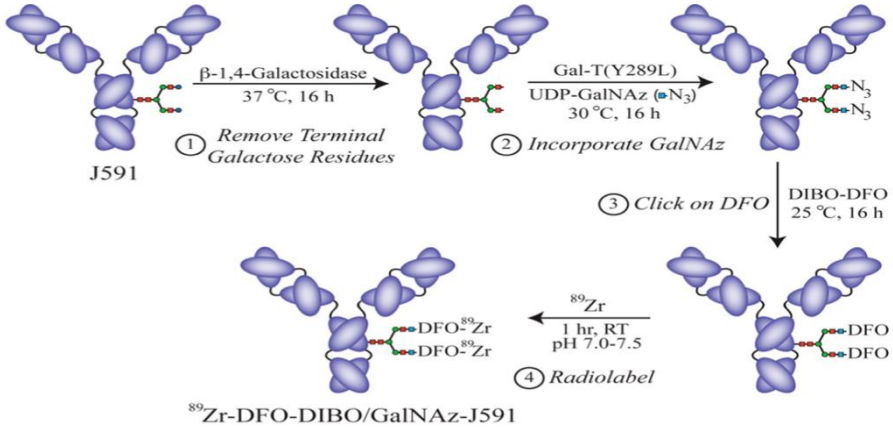
A. Afshar-Oromieh, et al, Eur J Nucl Med Mol Imaging (2013) 40:486–495

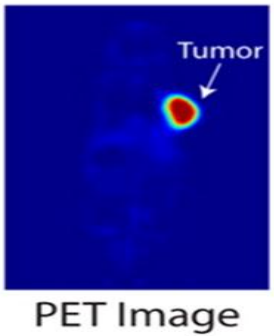
non site-specific



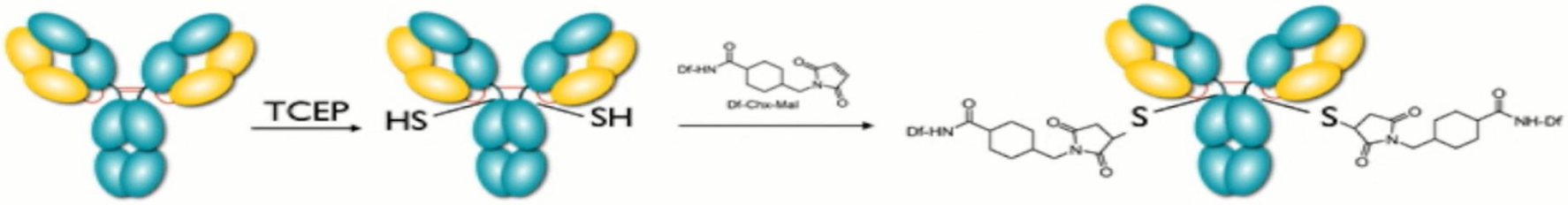


site-specific(via galactosidase)



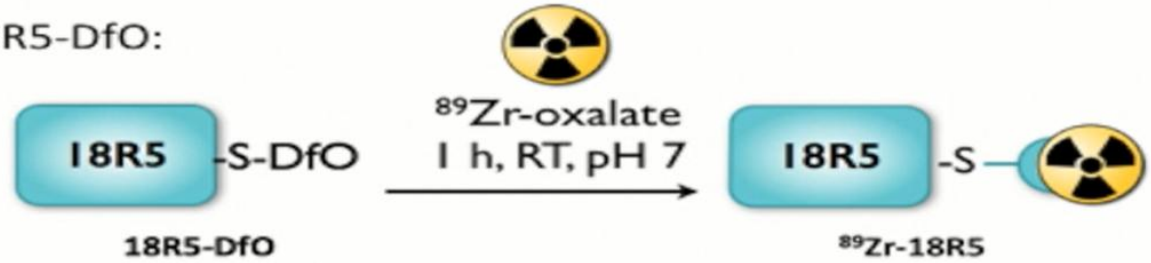


Brian M. Zeglis, et al, Bioconjugate Chem. 2011, 22, 2048–2059
Brian M. Zeglis, et al, Bioconjugate Chem. 2013, 24, 1057−1067



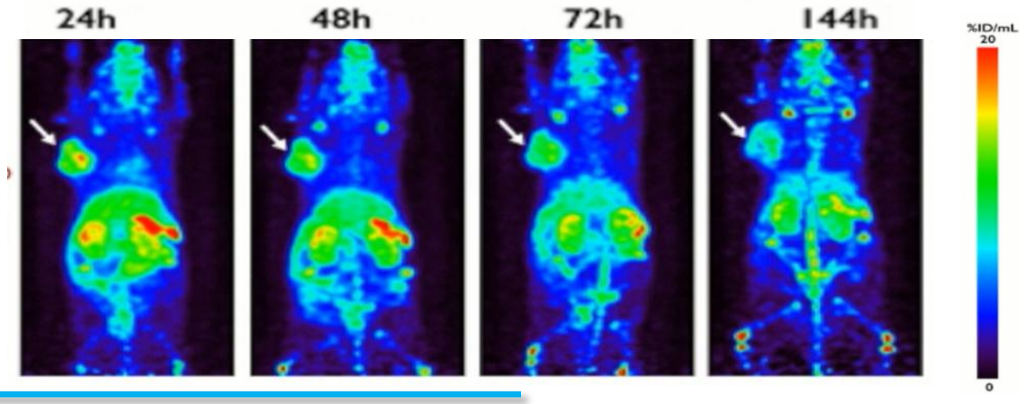
90% yield, approx 1.8 Df/IgG

- ^{89}Zr labeling of 18R5-DfO:



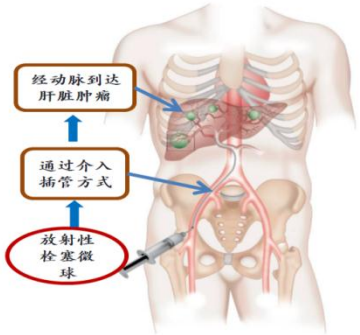
18R5-DfO

^{89}Zr-18R5

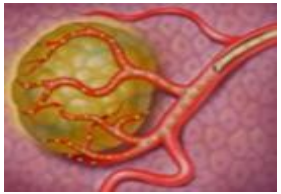


^{90}Y-microsphere Therapy

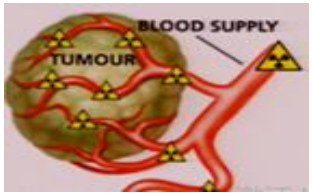
- Trans-arterial delivery of radioactive ^{90}Y-labeled microspheres via a catheter directly at disease sites (targeted infusion)
- Microspheres (20-30 μm) trapped in tumor capillary vessels due to their embolic size and targeted delivery

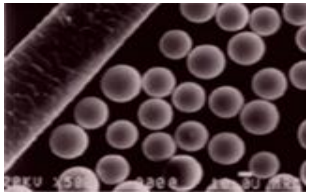


介入手术原理图

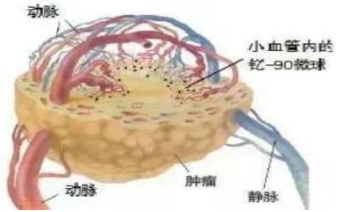


SIRTEX





TheraSphere



- β emission from trapped ^{90}Y-microspheres are capable of delivering lethal radiation doses to (proximal) neoplastic tissue while sparing (more distal) surrounding normal tissue

Commercial ^{90}Y-microsphere Products

	Sir Spheres	Thera-Spheres
Material	**Resin with bound Y-90**	**Glass, Y-90 in matrix**
Diameter	**20-60 micron**	**20-30 microns**
Activity per particle	**50 Bq**	**2500Bq**
Number of particles per dose (3GBq vial)	**40-80 million**	**1.2 million**
Available dose sizes	**3 GBq**	**3,5,7,10,15,20 GBq**
manufacturer	**Sirtex Medical, Australia**	**MDS Nordion , Canada**

Physical properties

- Mainly beta emitter: localized radiation effect while sparing normal adjacent liver tissues
- Mean energy: 0.93 MeV(2.27MeV maximum)
- Half-life: 64.1 hours (2.7 days)
- Effective duration of action: 14 days
- Range in tissue: 2.5mm (mean)/11mm(maximum)
- Small size of particles(25-45 μm) does not produce significant ischemic effect
- Permanent implant of microspheres
- Chemically inert, neither metabolized nor excreted

❖ 行业现状

国别	美国		英国		中国	
药典版本	USP23	USP28	BP1993	BP2003	CP2005	CP2015
注册总数	46	77	32	40	17	21
放射性药物产值（亿美元）	50		20		3	

❖ 国内主要生产企业情况

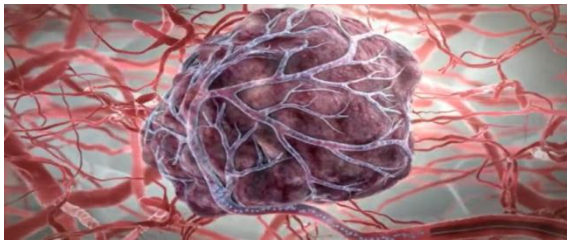
公司	产品	产值(亿)	利润(亿)
中核原子高科	(2014年)	6.4	1.7
成都中核高通	^{131}I\$^{60}Co$\$^{89}Sr$(2014年)	3.0	1.0
深圳海德威公司	尿素[14C]呼气试验药盒(2014年)	6.6	1.2
成都云克药业	类风湿药物(2016年)	3	1.3
GMS系列企业	放射性药盒类	2.5	0.5
江苏安迪科	18 F-FDG药品	2	0.8
智博高科	^{125}I 籽源	2.5	0.5
华神生物	碘[131I]美妥昔单抗注射液	0.3	0.1

企业少、竞争弱

四川省核工业地位

- 拥有36位院士领军的国内一流的核技术领域人才队伍。
- 拥有中国三座反应堆中的两座（核动力院493堆、九院的绵阳堆）
- 拥有中国核动力研究设计院、中国工程物理研究院、核工业西南物理研究院、四川大学等核技术（核医学）领军科研单位。
- 拥有成都云克药业、中核高通公司、成都华神集团等专业从事医用核素、放射性药品、医用放射性密封源以及放疗设备技术研究开发、产品生产及技术服务的企业。

总结——崇高的事业 智造的典范



❖ 成功的创业团队

- ✓ **公司首席专家**是中国放射性药物领域的领军科学家，**成都云克药业创始人**。**管理团队**在核技术应用领域创新与产业化方面有**丰富成功经验**。
- ✓ 核心技术团队包括1位工程院院士、2位“千人计划”学者；高级职称10余人；博士6人、硕士20余人，**充满情怀的科学家创业团队**。

❖ 系统的专利壁垒

- ✓ **自主知识产权**的高含量**磷-32玻璃微球**形成技术壁垒。
- ✓ **世界首创放射性炭微球**产品，可随时向患者提供治疗产品，实现癌症精准诊断和治疗。
- ✓ 放射性与生物技术的结合专利技术。

❖ 特殊的竞争壁垒

- ✓ 四川省具有**高通量反应堆的独特资源优势**（全国三座、四川拥有两座）。
- ✓ 四川省的核领域人才优势。
- ✓ 放射性微球**短半衰期**核素特点决定公司产品的竞争时间优势。

❖ 强大的平台支撑

- ✓ **国家级**“成都放射性药物检验**研究中心**”。
- ✓ **国家级**“放射性药物及同位素标记药物药理毒理**实验室**”

❖ 巨大的市场需求

- ✓ 超过百万的实体肿瘤患者。
- ✓ 预计销售收入40亿元**利润15亿元**以上。

请各位老师批评指正！

联系人：马欢

电话：15881180270

邮箱：942265493@qq.com