·综述·

整合素靶向放射性核素治疗进展

李永昊，柳江燕
（兰州大学第二医院核医学科，甘肃 兰州 730030）

摘　要：整合素 αvβ3 是肿瘤显像与治疗的重要靶点，其在肿瘤新生血管内皮细胞及多种恶性肿瘤细胞表面高表达，而在正常组织及静息内皮细胞中几乎不表达。基于 Arg-Gly-Asp（RGD）肽的正电子发射体层显像（PET）已广泛应用，但单靶点策略因肿瘤异质性而受限。β^- 核素标记 RGD 肽则存在摄取不足和肾脏蓄积问题。本文综述两大前沿方向的临床前进展：双靶点策略通过将整合素 αvβ3 与前列腺特异性膜抗原（PSMA）或成纤维细胞活化蛋白（FAP）等靶点联合，构建的异二聚体探针。临床前及临床研究表明，双靶点探针的肿瘤摄取、靶/背景比及病灶检出率均显著优于单靶点对照，有效克服了肿瘤异质性，提升肿瘤摄取与检出率；α 核素凭借高传能线密度与短射程，展现出优于 β^- 核素的抗肿瘤疗效。临床转化方面，镥-177 标记白蛋白结合-RGD 二聚体（^{177}Lu-AB-3PRGD$_2$）已完成首次人体研究，初步验证了整合素靶向放射性核素治疗的临床可行性，但其抗肿瘤活性有限。未来方向包括基于分子影像的患者筛选、双靶向分子结构优化、α 核素制剂开发。

关键词：整合素 αvβ3；放射性核素治疗；双靶点策略；α 核素；肿瘤诊疗一体化
中图分类号：R459.9　　**文献标志码：**A　　**文章编号：**1672-3554（2026）05-0799-10
DOI：10.11714/jsysu.med.YX20260102

Progress in Integrin Targeted Radionuclide Therapy

LI Yonghao，LIU Jiangyan
（Department of Nuclear Medicine，Lanzhou University Second Hospital，Lanzhou 730030，China）
Correspondence to：LIU Jiangyan；E-mail：Ery_liujy@lzu.edu.cn

Abstract： Integrin αvβ3 is an important target for tumor imaging and therapy. It is highly expressed on tumor neovascular endothelial cells and various malignant tumor cells，while being nearly absent in normal tissues and quiescent endothelial cells. Positron emission tomography（PET）based on Arg-Gly-Asp（RGD）peptides has been widely applied，yet single-target strategies are limited by tumor heterogeneity. β^- radionuclide-labeled RGD peptides exhibit problems of insufficient tumor uptake and renal accumulation. This review summarizes the preclinical progress in two frontier directions. Dual-targeting strategies combine integrin αvβ3 with prostate-specific membrane antigen（PSMA）or fibroblast activation protein（FAP）to construct heterodimeric probes. Preclinical and clinical studies have demonstrated that dual-targeting probes achieve significantly superior tumor uptake，target-to-background ratios，and lesion detection rates compared to single-target controls，effectively overcoming tumor heterogeneity and improving tumor uptake and detection rate. α radionuclides，by leveraging high linear energy transfer and short tissue range，demonstrate superior antitumor efficacy over β^-radionuclides. In terms of clinical translation，the albumin-binding RGD dimer labeled with lutetium-177（^{177}Lu-AB-3PRGD$_2$）has completed a first-in-human study，preliminarily validating the clinical feasibility of integrin-

收稿日期：2026-07-08　　**录用日期：**2026-09-14
基金项目：甘肃省科技计划项目（24JRRA922；26YFFA030）
作者简介：李永昊，第一作者，研究方向：SPECT/CT 影像诊断及核素治疗，E-mail：523281135@qq.com；柳江燕，通信作者，主任医师，博士生导师，研究方向：核素诊断及治疗，E-mail：Ery_liujy@lzu.edu.cn

targeted radionuclide therapy, albeit with limited antitumor activity. Future directions include molecular imaging-based patient selection, optimization of dual-targeting molecular structures, and development of α radionuclide formulations.

Key words: integrin αvβ3; radionuclide therapy; dual-targeting strategy; α radionuclides; cancer theranostics

[J SUN Yat-sen Univ(Med Sci),2026,47(5):799-808]

1941年,Hertz和Roberts首次将放射性碘用于甲亢患者,标志着放射性核素治疗的开端[1]。近年来Lutathera®([^{177}Lu]Lu-DOTATATE)、Pluvicto®([^{177}Lu]Lu-PSMA-617)用于神经内分泌肿瘤和转移性前列腺癌,证明了肽受体放射性核素治疗的临床价值[2]。整合素等新靶点由此成为研究热点[3]。

整合素是一类由α和β亚单位组成的跨膜糖蛋白,其中,αvβ3是研究最为深入的亚型之一[4]。αvβ3在肿瘤新生血管内皮细胞中高表达,而在静息内皮细胞中几乎不表达[5],其通过与含RGD序列蛋白结合,介导肿瘤细胞的黏附、迁移和侵袭[6]。基于RGD三肽序列的整合素靶向探针已广泛用于肿瘤显像[7]。然而,单靶点RGD显像存在局限性。在食管癌患者中,^{68}Ga-NODAGA-RGD对原发灶和转移淋巴结的检出率显著低于氟-18-氟代脱氧葡萄糖(^{18}F-fluorodeoxyglucose, ^{18}F-FDG),且肿瘤内摄取异质性明显[8]。这表明,仅靶向αvβ3单一分子难以准确反映肿瘤的生物学特征。研究者将整合素与另一肿瘤相关靶点联合,形成双靶点策略,提高靶向特异性[9]。

早期基于β$^-$核素的整合素靶向放射治疗存在肿瘤摄取不足、肾脏蓄积明显等缺陷[10]。整合素靶向小分子抑制剂cilengitide的Ⅲ期试验亦未能改善生存[11]。锕-225(Actinium-225, ^{225}Ac)、砹-211(Astatine-211, ^{211}At)为代表的α核素成为核素治疗的前沿方向。

尽管整合素靶向显像已获广泛验证,但其治疗应用仍面临三重挑战:①靶点异质性导致单靶点策略难以全面覆盖肿瘤病灶;②药代动力学不理想,RGD肽类在体内循环时间过短,肿瘤摄取及滞留不足;③单一治疗手段的疗效局限,传统β$^-$核素未能实现理想的抗肿瘤反应。针对上述挑战,研究者提出了双靶点策略和α核素联合治疗两大前沿方向。本文系统综述整合素靶向放射性核素治疗的最新进展,重点讨论双靶点策略、α核素药物设计及疗效评价,并展望未来发展方向。

1 靶向整合素的药物设计策略

整合素靶向放射性核素治疗的疗效依赖于放射性配体在肿瘤组织中的蓄积水平与滞留时间。RGD多肽对αvβ3整合素具有纳摩尔级亲和力[12]。但是,RGD在体内清除过快,肿瘤摄取有限。研究者从多聚化、药代动力学优化和双靶点设计这3个方向进行探索。

1.1 多聚化实现从单价到多价的亲和力提升

多价效应是提升受体亲和力的经典策略。多聚RGD肽可同时与多个整合素受体结合,形成"螯合效应",显著延缓配体从靶点解离。Mizuno等[13]比较了不同价数RGD肽的解离动力学,六价和四价RGD肽的解离速率常数均低于二价对照。Bozon-Petitprin等[14]构建了四价RAFT-RGD肽,标记钇-90(Yttrium-90, ^{90}Y)或^{177}Lu后在荷瘤小鼠中显著延缓肿瘤生长,验证了多聚RGD载体在放射治疗中的可行性。

王凡团队开发的^{99}-Tc-3PRGD$_2$对肺癌的诊断灵敏度达93%~97%,且其肿瘤摄取与整合素αvβ3表达水平及微血管密度呈正相关[15-16]。基于3PRGD$_2$结构开发的^{99}-Tc-3PRGD$_2$已于2026年4月获得中国国家药品监督管理局批准上市。作为全球首个获批的整合素αvβ3靶向放射性药物,该药的Ⅲ期临床试验(NCT04233476)证实,在肺部病灶良恶性鉴别上与^{18}F-FDG效果相当,而在肺癌淋巴结转移诊断中,其特异性和准确性显著优于^{18}F-FDG。这一突破证实了3PRGD$_2$二聚体设计的临床价值。然而,多聚化仍难以解决血液循环时间过短的问题,高剂量下肾脏摄取增加限制了其治疗应用。

1.2 药代动力学优化延长循环时间的策略

白蛋白结合可延长多肽类药物循环时间。Kazuta等[17]将白蛋白结合基序引入RGD肽,探针的血清蛋白结合率达86.5%。但是研究发现,单独引

入白蛋白结合基序会降低RGD肽对整合素的亲和力，通过引入双氨基酸连接子，亲和力可恢复。这说明连接子设计在平衡药效与药代动力学中具有关键作用。

针对αvβ6亚型，Huynh等[18]将白蛋白结合基团4-(对碘苯基)丁酸引入A20FMDV2线性肽，^{177}Lu标记后在胰腺癌模型中肿瘤摄取于1 h达6.12%ID/g，48 h仍维持在4.06%ID/g。单次27.8 MBq可显著抑制肿瘤生长，但伴明显体重下降；剂量增至37 MBq时则出现致死性肾毒性[18]。Ganguly等[19]采用新型环肽DOTA-5G并偶联白蛋白结合基团，单次74 MBq或分次2×37 MBq给药可显著延长中位生存期，且无体重下降。这表明，环肽设计的肾毒性更低。

与通过白蛋白结合策略不同，Zhang等[20]利用聚乙二醇自组装形成纳米颗粒，在不延长血循环的前提下实现长效肿瘤滞留，血液毒性风险较低。白蛋白结合策略通过延长血循环实现更高的肿瘤蓄积，但可能因延长血液循环时间而增加骨髓辐射暴露的风险。两种策略在疗效与安全性方面各具优势。

2　双靶点策略的临床前研究进展

Yan等[21]报道DOTA-FAPI-RGD异二聚体同时靶向FAP和αvβ3。在荷瘤小鼠中，[^{68}Ga]Ga-DOTA-FAPI-RGD的肿瘤摄取显著高于^{68}Ga-RGD及^{68}Ga-FAPI-04单靶点对照。Ocampo-García等[22]将PSMA与αvβ3联合，开发了^{225}Ac标记的异二聚体^{225}Ac-iPSMA-RGD，在结直肠癌模型中展现出α核素治疗潜力。

2.1　单靶点策略的局限性

2.1.1　病灶间异质性　Gondhane等[23]在甲状腺球蛋白升高、放射性碘显像阴性的甲状腺癌患者中评估了200个恶性转移灶。^{68}Ga-NODAGA-RGD检出率仅55%，而FDG检出率高达91%。软组织病灶的RGD检出率为53.19%，肺结节为50.76%，骨骼病灶为82.60%。

2.1.2　病灶内异质性　Dietz等[8]对食管或食管胃交界癌患者原发灶分析发现，^{68}Ga-NODAGA-RGD摄取呈现异质性分布，其中5例(56%)的摄取主要集中于肿瘤周边区域。^{18}F-FDG摄取在所有9例原发灶中均呈均匀分布。

2.2　代表性双靶点研究

目前多种双靶点组合已进入临床前及早期临床转化阶段(表1)。以PSMA与整合素αvβ3双靶点为例，示意了双靶向策略如何通过同时结合肿瘤细胞表面的不同抗原，以增强探针的肿瘤摄取并应对异质性。

2.2.1　前列腺特异性膜抗原与整合素双靶点　Ocampo-García等[22]制备的^{225}Ac-iPSMA-RGD在结肠癌模型中展现出显著延长的肿瘤滞留时间和远高于单靶点对照的吸收剂量。治疗11 d后，双靶点组肿瘤体积显著缩小，且未观察到肾毒性或肝损伤。Lu等[24]构建了靶向PSMA和整合素α2β1的环状双靶点分子cIP-L，并在雄激素依赖性、PSMA阳性的LNCaP细胞，以及雄激素非依赖性、PSMA阴性的PC-3细胞中验证了其特异性。PET/CT显像显示，^{68}Ga-cIP-L能清晰显示两种不同表型的前列腺癌肿瘤及微小转移灶。而单靶点探针无法同时显示上述两种表型的病灶[24]。目前尚无头对头研究直接比较αvβ3与α2β1作为PSMA第二靶点的优劣。

该组合的协同机制在于同时靶向肿瘤细胞(PSMA)和新生血管内皮(整合素αvβ3)。然而，Ocampo-García等[22]采用的结肠癌模型中αvβ3表达水平较低，双靶点优势主要来自PSMA部分，其在αvβ3高表达模型中的表现尚待验证。Lu等[24]构建的cIP-L虽在骨转移灶检出方面显示优势，但尚未进行疗效验证。目前该策略的证据主要来自临床前模型，缺乏临床研究数据。

2.2.2　成纤维细胞活化蛋白与整合素双靶点　Zhao等[25]比较了^{68}Ga-FAPI-RGD、^{18}F-FDG、^{68}Ga-FAPI-46在肿瘤患者中的显像性能。^{68}Ga-FAPI-RGD对原发肿瘤的检出灵敏度、肿瘤/背景比(tumor-to-background ratio，TBR)均高于^{18}F-FDG。与^{68}Ga-FAPI-46相比，双靶点探针在淋巴结、骨、肺及肝转移灶中的最大标准化摄取值(maximum standardized uptake value，SUVmax)、TBR均显著提高[25]。Wang等[26]对51例疑似肺肿瘤患者的研究同样证实^{68}Ga-FAPI-RGD对原发灶的检出率高于^{18}F-FDG，且在肿瘤中的摄取随时间延长而增加，而正常器官摄取逐渐下降。这显示其具备治疗转化的潜力。

表1 代表性双靶点策略比较

Table 1 Comparison of representative dual-targeting strategies

Targets	Radionuclide	Key results	References
PSMA+αvβ3	^{225}Ac	colon cancer model: tumor retention half-life 116 h; absorbed dose 237.07 Gy/37 kBq	[22]
PSMA+α2β1	^{68}Ga/^{177}Lu	prostate cancer bone metastasis model: detected micrometastases as small as 2 - 4 mm^3; false-negative rate as low as 1%	[24]
FAP+αvβ3	^{68}Ga	lung cancer patients (clinical): primary lesion detection rate 100% (FAPI-RGD) *vs* 84.2% (FDG); TBR increased ~3-fold	[25]
CD13+αvβ3	^{68}Ga	10 tumor models + Phase I clinical: tumor uptake 1.395 %ID/g; tumor-to-brain ratio 3.38	[28]
PD-L1+αvβ3	^{64}Cu	melanoma model: uptake 2.6 %ID/g; significant accumulation at 40 h post-injection	[33]
CXCR4+αvβ3	^{68}Ga	pancreatic cancer model: tumor uptake 2.54 %ID/g (2 h)	[34]
SSTR+αvβ3	^{68}Ga	GEP-NET patients: *vs* ^{68}Ga-DOTATATE, liver metastases detected 634 *vs* 532; tumor/liver ratio 8.4 *vs* 4.7	[35]
GRPR+αvβ3	^{68}Ga	breast cancer / brain tumor patients: breast cancer detection rate 100%; high-grade glioma detection rate 95%	[36-37]

该策略同时靶向肿瘤相关成纤维细胞和新生血管,可实现“基质+血管”双重干预。Zhao等[25]和Wang等[26]的临床显像已初步验证其优势,但甲状腺和胰腺的生理性高摄取可能掩盖邻近病灶。这提示,若将该策略拓展至治疗应用,正常组织对辐射剂量的耐受性将成为直接限定其临床转化可行性的关键问题。

2.2.3 *氨基肽酶N与整合素双靶点* CD13(氨基肽酶N)与αvβ3均为肿瘤新生血管标志物。Gai等[27]证实,靶向αvβ3和CD13的异二聚体^{68}Ga-NGR-RGD在乳腺癌模型中肿瘤摄取显著优于单靶点。Lü等[28]证实^{68}Ga-HX01在胰腺癌、乳腺癌及胆囊癌模型中呈现高摄取,在原位胶质瘤模型中TBR显著高于^{18}F-FDG。双靶点探针的肿瘤摄取显著高于单靶点对照[28]。^{68}Ga-HX01获NMPA批准进入Ⅰ期临床试验。2项独立Ⅰ期研究在人体中验证了^{68}Ga-HX01靶向特异性及安全性[29-30]。^{68}Ga-HX01在显像层面的成功验证了CD13/αvβ3双靶点的临床靶向可行性,但显像剂的快速血液清除特性(半衰期约29 min)却难以满足治疗性核素对循环时间的需求。为提升肿瘤摄取和滞留时间,Yang等通过引入不同白蛋白结合基团构建了^{177}Lu标记的L6和L21[31-32]。2款药物通过白蛋白结合策略显著增强了肿瘤摄取并延长了滞留时间。二者相比较,L21的摄取峰值更高,而L6的滞留更持久。

该策略利用CD13与αvβ3在新生血管上共表达的特点实现协同靶向。但是,HX01在体内的快速清除限制了其治疗应用。通过白蛋白结合策略虽优化了药代动力学[31-32],但能否在延长循环与降低正常器官辐射暴露之间取得平衡,是该策略向临床治疗转化的关键难题。

2.2.4 *其他新兴双靶点组合* 程序性死亡配体1(programmed death-ligand 1, PD-L1)/整合素、CXC趋化因子受体4(C-X-C chemokine receptor type 4, CXCR4)/整合素及生长抑素受体(somatostatin receptor, SSTR)/整合素等双靶点策略亦取得进展。Liu等[33]发现,^{64}Cu标记的PD-L1/RGD,在黑色素瘤模型中注射后40 h,肿瘤部位仍有显著的积聚。Jiang等[34]开发了靶向CXCR4与αvβ3的^{68}Ga-yG5-RGD,在胰腺癌模型中,其肿瘤摄取显著优于单靶点,但正常肝组织摄取较高。Jiang等[35]在35例胃肠胰神经内分泌肿瘤患者中比较了双靶点探针^{68}Ga-NOTA-3P-TATE-RGD与SSTR单靶点探针^{68}Ga-DOTATATE的显像效能。双靶点探针在肝

转移灶检出数量、TBR均显著优于单靶点探针[35]。这说明，单一SSTR靶向在高级别神经内分泌肿瘤中灵敏度有限，联合整合素靶向可弥补这一缺陷。针对胃泌素释放肽受体（gastrin-releasing peptide receptor，GRPR）与整合素双靶点[36-37]，Wen等[36]开发的^{68}Ga-RGD-RM26-03在11例乳腺癌患者中检出率为100%。Wen等[36]和Wang等[37]开发的GRPR/整合素双靶点探针在乳腺癌和脑胶质瘤中均实现了高检出率和较高的TBR。

不同双靶点组合在各自模型中均显示出相较于单靶点的优势，表明双靶向设计在扩大病灶检出范围方面具有潜力。然而，不同组合的临床转化进程存在明显差异：PD-L1/整合素和CXCR4/整合素策略仍处于临床前模型验证阶段。SSTR/整合素策略已在神经内分泌肿瘤患者中获得初步临床显像证据，但尚未拓展至治疗领域。GRPR/整合素策略中，胰腺生理性高摄取是制约其应用的主要因素。上述差异提示，各组合的适用肿瘤类型及转化前景不同，其选择需综合靶点表达谱与正常组织分布特征。

3　α核素在靶向整合素治疗中的临床前研究

α核素因其高传能线密度及短射程特性，对乏氧和耐药肿瘤同样有效[38-40]。PSMA靶向α核素治疗已进入临床试验阶段[41-42]。一项1 155例的荟萃分析显示，^{225}Ac-PSMA治疗的PSA50反应率（即PSA下降≥50%的比例）达65%[43]。而整合素靶向α核素治疗仍处于临床前探索期。

3.1　抗肿瘤疗效及联合治疗策略

多项研究证实，α核素标记的RGD多聚体具有明确的抗肿瘤活性。Yoshimoto等[44]制备的^{225}Ac标记二聚体RGD肽在胰腺癌模型中肿瘤滞留长达168 h，单次65~90 kBq即将中位生存期从63 d延长至112~126 d。

Echigo等[45]在原位胶质母细胞瘤模型中评估了^{211}At-RGD药物。结果显示，药物能选择性蓄积于脑内肿瘤区域（TBR达16.6），单次静脉注射270 kBq即可显著延长小鼠的生存期。该研究首次在颅内模型中验证了整合素靶向α核素治疗的有效性。在联合免疫治疗方面，Echigo等[46]进一步评估了^{211}At-RGD与抗细胞毒性T淋巴细胞相关蛋白4抗体（anti-cytotoxic T-lymphocyte-associated protein 4 antibody，CTLA-4）的协同效应。在免疫健全的荷瘤小鼠中，^{211}At-RGD联合抗CTLA-4抗体治疗显著延长了生存期，并显著提高了CD8^{+}T细胞浸润比例[46]。该研究首次在静脉注射的靶向α治疗体系中证实整合素靶向α核素治疗可诱发免疫原性细胞死亡，为临床联合方案的设计提供了依据。Yoshimoto等[47]在相同分子平台直接比较了^{225}Ac与^{177}Lu的疗效与安全性（表2）。此外，Liu等[48]构建的^{211}At标记血管内皮生长因子受体/整合素异二聚体同样在胶质瘤模型中显著延长了中位生存期。目前应用最广的两种α核素^{225}Ac与^{211}At在物理性质上差异显著。^{225}Ac半衰期9.9 d，便于远距离运输和长时间辐照，但其衰变链中多个子体的再分布所增加的正常器官辐射可能限制其应用。^{211}At半衰期仅7.2 h，与RGD肽的清除动力学更为匹配，但At-C键的体内稳定性是其化学层面的主要挑战。生产供应方面，^{225}Ac可通过^{229}Th/^{225}Ac发生器或加速器途径获得，^{211}At则依赖回旋加速器生产，二者供应能力均十分有限，直接限制了α核素的广泛应用。

3.2　安全性评估

α核素治疗的安全性问题主要有以下2个方面：①核素固有的子体再分布。Josefsson等[49]发现，^{225}Ac-cRGDfK产生的子体^{221}Fr和^{213}Bi对肾脏总吸收剂量的占比高达35%，其中^{213}Bi占比约27%，^{221}Fr占比约8%。^{213}Bi经肾排泄并滞留于肾小管，是肾脏辐射负担的主要来源。^{221}Fr具有亲骨性，主要沉积于骨表面，股骨吸收剂量系数达20.7 mGy/kBq，提示骨髓为重要的受累器官。此外，肝脏释放的游离^{213}Bi可进一步加重肾脏辐射负担。因此，载体设计既要考虑子体滞留能力以减轻肾毒性，也需关注游离^{221}Fr对骨髓的潜在风险[49]。②药代动力学调控。白蛋白结合策略虽能提升肿瘤摄取，但血液清除过慢对短半衰期α核素构成挑战。Echigo等[50]在含白蛋白结合基团的^{211}At-RGD基础上提出了“先蓄积、后清除”的动态调控策略。于药物充分肿瘤蓄积后（注射后1 h）给予白蛋白结合抑制剂，竞争性置换结合于白蛋白的药物，加速其从血液和正常组织清除。结果显示，血液半衰期从50.7 h缩

表2 ^{225}Ac与^{177}Lu标记PD-RGD在同一分子平台上的疗效与安全性比较

Table 2 Comparison of efficacy and safety between ^{225}Ac- and ^{177}Lu-labeled PD-RGD on the same molecular platform

Parameter	^{225}Ac-PD-RGD	^{177}Lu-PD-RGD
Dose	40 kBq	40 MBq
Tumor suppression	Comparable	Comparable
Major toxicity	Hepatotoxicity	No significant toxicity
half-life	9.9 d	6.7 d
Radiation type	α-emitter	β-emitter
Reference	[47]	[47]

The administered activities of ^{225}Ac and ^{177}Lu (40 kBq vs 40 MBq) were experimental doses selected by Yoshimoto et al. to achieve comparable antitumor effects on the same molecular platform, and are not clinical equivalent doses. Given the intrinsic differences in physical half-life and decay mode between the two radionuclides, this comparison provides relative reference only under the same molecular carrier and animal model conditions, and should not be extrapolated as clinical equivalence between the two nuclides.Half-life refers to physical half-life.

短至27.7 min,而肿瘤吸收剂量未受影响,肿瘤/肾脏比从2.01提高至2.73。该策略在保证疗效的同时降低了正常组织辐射暴露,为α核素的剂量优化提供了新手段。

整合素靶向α核素治疗兼具物理靶向精准和生物学杀伤高效的优势,但尚无首次人体研究报道,子体再分布导致的肾毒性等是当前主要瓶颈。此外,^{211}At的生产依赖回旋加速器[^{209}Bi(α,2n)^{211}At反应],全球供应点稀少,At-C键的体内稳定性亦有待提升。这些物理化学层面的瓶颈同样制约着临床转化进程。

4 临床转化现状与展望

4.1 首次人体研究

Sui等[51]开展了^{177}Lu-AB-3PRGD2在整合素αvβ3阳性晚期肿瘤患者中的首次人体研究,共纳入10例患者(8例腺样囊性癌、1例肝内胆管癌、1例子宫平滑肌肉瘤),单次静脉注射剂量为(1.56±0.08) GBq。血液半衰期为(2.85±2.17) h。肾脏吸收剂量为(0.684±0.132) mGy/MBq,膀胱壁吸收剂量为(1.852±1.047) mGy/MBq。安全性方面,未观察到4级或5级毒性;3例患者出现不良事件,其中1例出现3级丙氨酸氨基转移酶和天冬氨酸氨基转移酶升高,后自行恢复。然而其疗效有限,根据RECIST1.1标准,9例为疾病稳定、1例为疾病进展;根据PERCIST 1.0标准,1例为部分缓解(子宫平滑肌肉瘤患者盆腔淋巴结转移灶SUVmax从12.0降至4.6)、8例为疾病稳定、1例为疾病进展[51]。这一结果揭示,即使在二聚体与白蛋白结合的优化策略下,单次低剂量的^{177}Lu治疗仍难以实现强劲的抗肿瘤反应,靶向整合素的放射性核素治疗可能需要更高的累积剂量或α核素才能突破疗效瓶颈。

4.2 总结与展望

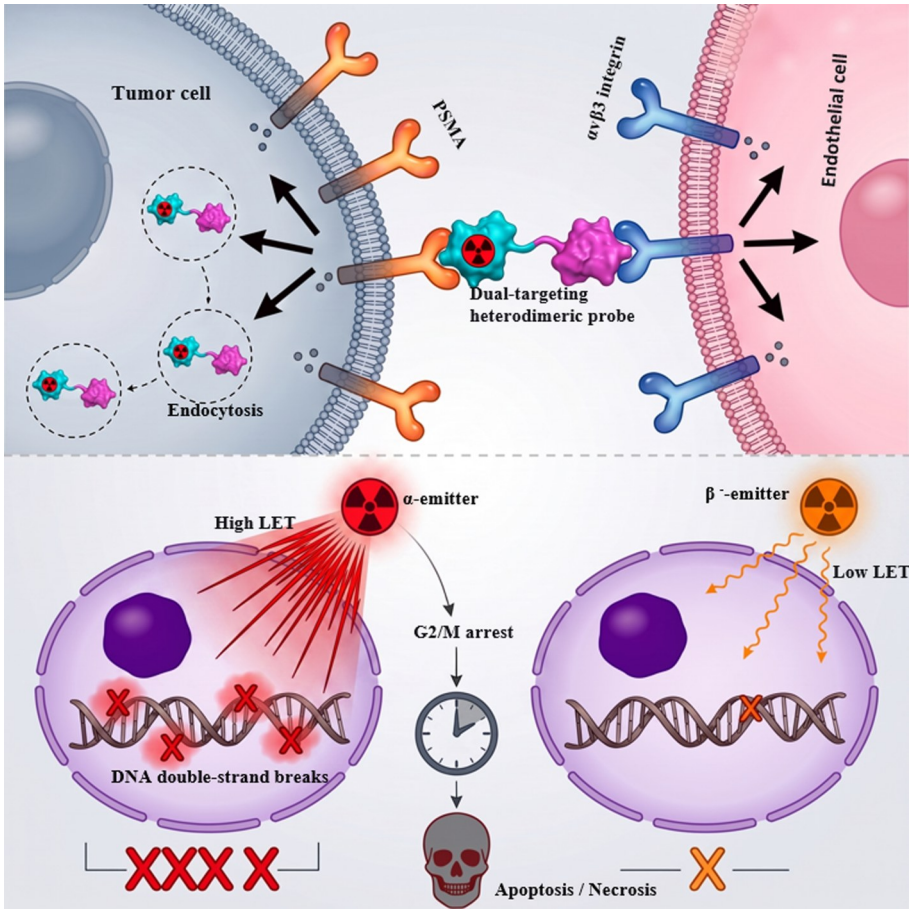
研究显示^{177}Lu-PSMA-617可将总生存期从11.3个月延长至15.3个月[52];PSMAfore试验中,^{177}Lu-PSMA-617治疗的中位影像学无进展生存期较更换雄激素受体通路抑制剂方案延长近1倍(11.6个月 *vs.* 5.6个月)[53];NETTER-2试验证实,^{177}Lu-DOTATATE一线治疗高级别GEP-NETs的中位无进展生存期显著长于高剂量奥曲肽(22.8个月 *vs.*8.5个月)[54]。这些成功为整合素靶向治疗提供了重要参照。

整合素靶向α核素治疗的转化需重点关注:①患者筛选:cilengitide在Ⅲ期试验中因患者筛选不足而失败[11]。基于^{68}Ga或^{18}F标记RGD探针的PET/CT可定量评估肿瘤整合素表达水平及异质性,筛选出可能从整合素靶向α核素治疗中获益的患者。②分子设计优化与肾毒性防护。Rheinfrank等[55]发现,^{177}Lu标记的αvβ6-RGD三聚体的肿瘤/血液比(112)远高于二聚体(54)和四聚体(10.4),且琥珀酰明胶可使肾脏摄取降低89%。琥珀酰明胶降低肾脏摄取61%~85%,肿瘤/肾脏比提高2.6~3.3倍,效果优于精氨酸/赖氨酸(20%~41%),且琥珀酰明

胶严重过敏反应发生率与临床常规造影剂相当，提示临床转化可行[56]。③联合免疫治疗：TRT可上调肿瘤PD-L1表达。Chen等[57]证实，^{177}Lu-EB-RGD与抗PD-L1同时给药时肿瘤完全消退率达80%，且治愈小鼠对同种肿瘤再挑战产生完全排斥。Shi等[58]发现，^{177}Lu-AB-3PRGD$_2$治疗后PD-L1表达在肿瘤浸润免疫细胞中第3~6天达峰，在表达上调窗口期给予单次抗PD-L1治疗即可实现与多次给药相当的协同疗效。

放射性药物的传统研发高度依赖试错筛选，效率有限。近年来，分子对接、分子动力学模拟及人工智能驱动方法已逐步融入靶向放射性药物的理性设计过程[59]。针对整合素αvβ3靶向的RGD肽，Pirooznia等[60]将RGD肽对接至αvβ3晶体结构，经分子动力学模拟，从多种构象中筛选出最稳定候选分子。此外，生成式AI模型与分子数据库的联合应用已在放射性药物领域展现出潜力，如基于深度学习的虚拟筛选可加速金属-螯合剂匹配及肽类配体的从头设计，而高通量分子动力学模拟与AI驱动的结合自由能预测正在成为优化连接子长度与白蛋白结合基团组合的高效工具。未来，这些计算工具的深度整合有望拓展RGD模拟肽及双靶点异二聚体的化学空间，加速新一代整合素靶向放射性药物的研发。

目前，^{177}Lu-AB-3PRGD$_2$等整合素靶向药物的剂量递增研究已完成。而以^{225}Ac/^{211}At标记的双靶点分子也完成临床前安全评估。将双靶点策略的广谱识别优势与α核素的高效杀伤特性相融合是推动该领域迈向首次人体α核素治疗试验的关键路径。二者协同作用的机制如（图1）所示：双靶向α核素探针经受体介导内化入胞，释放的高能α粒子诱发DNA双链断裂，最终驱动肿瘤细胞死亡。



PSMA: prostate-specific membrane antigen; integrin αvβ3: integrin alpha-V beta-3; LET: linear energy transfer; G2/M: G2/mitosis phase.

图1　双靶点策略靶向整合素αvβ3治疗机制示意图（以PSMA/整合素αvβ3双靶点为例）

Fig. 1　Schematic of dual-targeting strategy in integrin αvβ3-targeted therapy (exemplified by PSMA/integrin αvβ3 dual targeting)

参考文献

[1] Mihailovic J. Evolving paradigm in radioactive iodine therapy for differentiated thyroid cancer: historical perspectives, current practices and future directions [J]. Diagnostics (Basel), 2025, 15(11): 1438-1466.

[2] Tran HH, Yamaguchi A, Manning HC. Radiotheranostic landscape: a review of clinical and preclinical development [J]. Eur J Nucl Med Mol Imaging, 2025, 52(7): 2685-2709.

[3] 王立琴, 柳江燕. ^{225}Ac在肿瘤靶向治疗中的应用及进展[J]. 中山大学学报(医学科学版), 2024, 45(4): 503-510.
Wang LQ, Liu JY. Application and research progress of ^{225}Ac in tumor targeted treatment[J]. J Sun Yat-sen Univ(Med Sci), 2024, 45(4): 503-510.

[4] 中华医学会核医学分会, 中国生物物理学会分子影像学分会. 整合素RGD受体显像临床应用专家共识(2022版)[J]. 协和医学杂志, 2022, 13(2): 227-234.
Chinese Society of Nuclear Medicine, Chinese Society of Molecular Imaging in Chinese Biophysical Society. Expert consensus on clinical application of integrin RGD receptor imaging (2022)[J]. Med J PUMCH, 2022, 13(2): 227-234.

[5] Chen H, Niu G, Wu H, et al. Clinical application of radiolabeled RGD peptides for PET imaging of integrin alphavbeta3[J]. Theranostics, 2016, 6(1): 78-92.

[6] Badipa F, Alirezapour B, Yousefnia H. An overview of radiolabeled RGD peptides for theranostic applications [J]. Curr Radiopharm, 2023, 16(2): 107-122.

[7] Fu J, Xie Y, Fu T, et al. [(99m)Tc]Tc-Galacto-RGD(2) integrin alpha(v)beta(3)-targeted imaging as a surrogate for molecular phenotyping in lung cancer: real-world data [J]. EJNMMI Res, 2021, 11(1): 59-72.

[8] Dietz M, Dunet V, Mantziari S, et al. Comparison of integrin alpha(v)beta(3) expression with (68)Ga-NODAGA-RGD PET/CT and glucose metabolism with (18)F-FDG PET/CT in esophageal or gastroesophageal junction cancers [J]. Eur J Hybrid Imaging, 2023, 7(1): 3-15.

[9] Hu M, Zhang C, Fan D, et al. Advances in preclinical research of theranostic radiopharmaceuticals in nuclear medicine [J]. ACS Appl Mater Interfaces, 2025, 17(3): 4337-4353.

[10] Liu Z, Wang F, Chen X. Integrin targeted delivery of radiotherapeutics[J]. Theranostics, 2011, 1: 201-210.

[11] Echavidre W, Picco V, Faraggi M, et al. Integrin-alphavbeta3 as a therapeutic target in glioblastoma: back to the future?[J]. Pharmaceutics, 2022, 14(5): 1053-1065.

[12] Alipour M, Baneshi M, Hosseinkhani S, et al. Recent progress in biomedical applications of RGD-based ligand: from precise cancer theranostics to biomaterial engineering: a systematic review[J]. Biomed Mater Res A, 2019, 108(4): 839-850.

[13] Mizuno Y, Suebboonprathueng T, Onoe S, et al. Design of a tetravalent RGD peptide capable of simultaneous binding with multiple integrin alphavbeta3 for targeted radionuclide therapy [J]. J Med Chem, 2025, 68(6): 6518-6533.

[14] Bozon-Petitprin A, Bacot S, Gauchez AS, et al. Targeted radionuclide therapy with RAFT-RGD radiolabelled with (90)Y or (177)Lu in a mouse model of alphavbeta3-expressing tumours[J]. Eur J Nucl Med Mol Imaging, 2015, 42(2): 252-263.

[15] Shi J, Fan D, Dong C, et al. Anti-tumor effect of integrin targeted (177)Lu-3PRGD2 and combined therapy with Endostar[J]. Theranostics, 2014, 4(3): 256-266.

[16] Xiao L, Xin J. Advances in clinical oncology research on (99m)Tc-3PRGD2 SPECT imaging[J]. Front Oncol, 2022, 12: 898764.

[17] Kazuta N, Nakashima K, Watanabe H, et al. Development of novel integrin alpha(v)beta(3)-targeted radioligand for enhanced tumor accumulation [J]. ACS Med Chem Lett, 2025, 16(7): 1346-1353.

[18] Huynh TT, Sreekumar S, Mpoy C, et al. Therapeutic efficacy of 177Lu-labeled A20FMDV2 peptides targeting αvβ6 [J]. Pharmaceuticals, 2022, 15(2): 229-241.

[19] Ganguly T, Bauer N, Davis RA, et al. Preclinical evaluation of (68)Ga- and (177)Lu-labeled integrin alpha(v)beta(6)-targeting radiotheranostic peptides[J]. J Nucl Med, 2023, 64(4): 639-644.

[20] Zhang S, Ma X, Wu J, et al. Enhanced radiotheranostic targeting of integrin alpha5beta1 with PEGylation-enabled peptide multidisplay platform (PEGibody): a strategy for prolonged tumor retention with fast blood clearance[J]. Acta Pharm Sin B, 2025, 15(2): 692-706.

[21] Yan Q, Zhong J, Liu Y, et al. Synthesis and preclinical evaluation of a heterodimeric radioligand targeting fibroblast activation protein and integrin-alpha(v)beta(3)[J]. Eur J Med Chem, 2023, 251: 115279.

[22] Ocampo-Garcia B, Cruz-Nova P, Jimenez-Mancilla N, et al. (225)Ac-iPSMA-RGD for alpha-therapy dual targeting of stromal/tumor cell PSMA and integrins[J]. Int J Mol Sci, 2023, 24(23): 16553-16573.

[23] Gondhane A, Verma P, Chandak A, et al. Prospective evaluation of 68Ga-NODAGA-RGD PET-CT in patients of carcinoma thyroid with thyroglobulin elevated negative

radioiodine scintigraphy (TENIS) with a head-to-head comparison with FDG-PET/CT [J]. Nucl Med Commun, 2024, 45(5): 412-419.

[24] Lu X, Li W, Xi C, et al. Construction and evaluation of PSMA and integrin α2β1 targeted hetero-bivalent agents for the PET imaging and internal irradiation therapy of prostate cancer[J]. Chem Eng J, 2025, 505: 158570.

[25] Zhao L, Wen X, Xu W, et al. Clinical evaluation of (68)Ga-FAPI-RGD for imaging of fibroblast activation protein and integrin alpha(v)beta(3) in various cancer types[J]. J Nucl Med, 2023, 64(8): 1210-1217.

[26] Wang R, Jakobsson V, Wang J, et al. Dual targeting PET tracer Ga-FAPI-RGD in patients with lung neoplasms: a pilot exploratory study [J]. Theranostics, 2023, 13(5): 2979-2992.

[27] Gai Y, Jiang Y, Long Y, et al. Evaluation of an integrin alpha (v) beta (3) and aminopeptidase N dual-receptor targeting tracer for breast cancer imaging[J]. Mol Pharm, 2020, 17(1): 349-358.

[28] Lü X, Song X, Long Y, et al. Preclinical evaluation of a dual-receptor targeted tracer [(68) Ga] Ga-HX01 in 10 different subcutaneous and orthotopic tumor models[J]. Eur J Nucl Med Mol Imaging, 2023, 51(1): 54-67.

[29] Zhang X, Fang H, Yang B, et al. Phase I study of [(68)Ga] Ga-HX01 for targeting integrin alphavbeta3 and CD13 in healthy and malignancy subjects [J]. Eur J Nucl Med Mol Imaging, 2025, 52(4): 1293-1304.

[30] Zhang X, Yang B, Qin C, et al. Clinical translation of a dual-integrin αvβ3- and CD13-targeting PET tracer[J]. Clin Nucl Med, 2025, 50(4): 332-337.

[31] Yang B, Shan C, Lin Z, et al. Preparation and evaluation of a novel albumin-binding heterodimer therapeutic radiopharmaceutical with remarkable tumor accumulation and retention [J]. Eur J Med Chem, 2025, 290: 117589.

[32] Yang B, Shan C, Song X, et al. Development and evaluation of albumin binder-conjugated heterodimeric radiopharmaceuticals targeting integrin alpha(v)beta(3) and CD13 for cancer therapy[J]. Eur J Nucl Med Mol Imaging, 2024, 51(11): 3334-3345.

[33] Liu W, Yuan X, Zhang S, et al. Dual-targeting of PD-L1 and integrin alpha(v)beta(3) for preclinical PET imaging of cancer[J]. Chembiochem, 2025, 26(18): e202500508.

[34] Jiang Y, Long Y, Ji H, et al. Development and evaluation of a peptide heterodimeric tracer targeting CXCR4 and integrin alpha (v) beta (3) for pancreatic cancer imaging [J]. Pharmaceutics, 2022, 14(9): 1791-1806.

[35] Jiang Y, Liu Q, Wang G, et al. A prospective head-to-head comparison of 68Ga-NOTA-3P-TATE-RGD and 68Ga-DOTATATE in patients with gastroenteropancreatic neuroendocrine tumours[J]. Eur J Nucl Med Mol Imaging, 2022, 49(12): 4218-4227.

[36] Wen X, Wang R, Xu P, et al. Synthesis, preclinical, and initial clinical evaluation of integrin alpha(V)beta(3) and gastrin-releasing peptide receptor (GRPR) dual-targeting radiotracer [(68) Ga] Ga-RGD-RM26-03 [J]. Eur J Nucl Med Mol Imaging, 2024, 51(7): 2023-2035.

[37] Wang R, Li Z, Wang L, et al. Clinical translation of a dual integrin-and GRPR-targeting PET radiotracer 68Ga-DOTA-RGD-RM26 in glioma[J]. Clin Nucl Med, 2026, 51(2): 115-122.

[38] Zuo D, Wang H, Yu B, et al. Astatine-211 and actinium-225: Two promising nuclides in targeted alpha therapy [J]. Acta Biochim Biophys Sin (Shanghai), 2024, 57(3): 327-343.

[39] Rabiei M, Asadi M, Yousefnia H. Astatine-211 radiopharmaceuticals; Status, trends, and the future [J]. Curr Radiopharm, 2024, 17(1): 7-13.

[40] Munekane M, Fuchigami T, Ogawa K. Recent advances in the development of (225) Ac- and (211) At-labeled radioligands for radiotheranostics [J]. Anal Sci, 2024, 40(5): 803-826.

[41] Schatz CA, Zitzmann-Kolbe S, Moen I, et al. Preclinical efficacy of a PSMA-targeted actinium-225 conjugate (225Ac-Macropa-Pelgifatamab): a targeted alpha therapy for prostate cancer [J]. Clin Cancer Res, 2024, 30(11): 2531-2544.

[42] Watabe T, Naka S, Shirakami Y, et al. Development of PSMA-targeted alpha therapy using [(211)At]PSMA-5[J]. Semin Nucl Med, 2025, 55(6): 947-954.

[43] Ninatti G, Scilipoti P, Pini C, et al. Time for action: Actinium-225 PSMA-targeted alpha therapy for metastatic prostate cancer - a systematic review and meta-analysis [J]. Theranostics, 2025, 15(8): 3386-3399.

[44] Yoshimoto M, Washiyama K, Ohnuki K, et al. Long-term therapeutic effects of (225)Ac-DOTA-Ec(RGDfK) induced by radiosensitization via G2/M arrest in pancreatic ductal adenocarcinoma[J]. Pharmaceutics, 2024, 17(1): 9-26.

[45] Echigo H, Munekane M, Fuchigami T, et al. Evaluation of an (211) At-labeled RGD peptide in an orthotopic glioblastoma model by targeted alpha therapy [J]. Nucl Med Biol, 2025, 150-151: 109572.

[46] Echigo H, Munekane M, Fuchigami T, et al. Combination therapy of an (211) At-labeled RGD peptide and immune checkpoint blockade to enhance antitumor efficacy [J]. Eur J

Nucl Med Mol Imaging, 2026, 53(2): 992-1003.

[47] Yoshimoto M, Wada SI, Yoshii Y, et al. Enhanced radionuclide therapy via the conjugation of pentadecanoic acids with 225Ac- and 177Lu-labeled RGD peptides [J]. Cancer Sci, 2025, 117(1): 193-202.

[48] Liu W, Ma H, Liang R, et al. Targeted alpha therapy of glioma using 211At-labeled heterodimeric peptide targeting both VEGFR and integrins [J]. Mol Pharm, 2022, 19(9): 3206-3216.

[49] Josefsson A, Cortez AG, Yu J, et al. Evaluation of targeting alpha(V)beta(3) in breast cancers using RGD peptide-based agents[J]. Nucl Med Biol, 2024, 128-129: 108880.

[50] Echigo H, Munekane M, Fuchigami T, et al. Optimizing the pharmacokinetics of an 211At-labeled RGD peptide with an albumin-binding moiety via the administration of an albumin-binding inhibitor[J]. Eur J Nucl Med Mol Imaging, 2024, 51(9): 2663-2671.

[51] Sui H, Guo F, Liu H, et al. Safety, pharmacokinetics, and dosimetry of (177) Lu-AB-3PRGD2 in patients with advanced integrin alpha(v)beta(3)-positive tumors: a first-in-human study [J]. Acta Pharm Sin B, 2025, 15(2): 669-680.

[52] Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer [J]. N Engl J Med, 2021, 385(12): 1091-1103.

[53] Morris MJ, Castellano D, Herrmann K, et al. 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial [J]. Lancet, 2024, 404(10459): 1227-1239.

[54] Singh S, Halperin D, Myrehaug S, et al. [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study [J]. Lancet, 2024, 403(10446): 2807-2817.

[55] Rheinfrank T, Lebruška V, Stangl S, et al. Three is a magic number: Tailored clickable chelators used to determine optimal RGD-peptide multiplicity in αvβ6-integrin targeted 177Lu-labeled cancer theranostics [J]. Bioconjugate Chem, 2024, 35(12): 1970-1984.

[56] Stangl S, Nguyen NT, Brosch-Lenz J, et al. Efficiency of succinylated gelatin and amino acid infusions for kidney uptake reduction of radiolabeled αvβ6-integrin targeting peptides: Considerations on clinical safety profiles [J]. Eur J Nucl Med Mol Imaging, 2024, 51(11): 3191-3201.

[57] Chen H, Zhao L, Fu K, et al. Integrin αvβ3-targeted radionuclide therapy combined with immune checkpoint blockade immunotherapy synergistically enhances anti-tumor efficacy[J]. Theranostics, 2019, 9(25): 7948-7960.

[58] Shi J, Gao H, Wu Y, et al. Nuclear imaging of PD-L1 expression promotes the synergistic antitumor efficacy of targeted radionuclide therapy and immune checkpoint blockade [J]. Eur J Nucl Med Mol Imaging, 2025, 52(3): 955-969.

[59] Gervasoni S, Guccione C, Malloci G. Computational studies of target-specific radiopharmaceuticals for theranostics [J]. J Mol Graph Model, 2026, 143: 109264.

[60] Pirooznia N, Abdi K, Beiki D, et al. Radiosynthesis, biological evaluation, and preclinical study of a ^{68}Ga-labeled cyclic RGD peptide as an early diagnostic agent for overexpressed αvβ3 integrin receptors in non-small-cell lung cancer [J]. Contrast Media Mol Imaging, 2020, 2020: 8421657.

(编辑 黄子芸)