抗肿瘤抗生素药物制剂的研究进展

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摘要: 抗肿瘤抗生素在抗肿瘤方面具有巨大的应用潜力, 目前已有一些药物被成功开发, 成为临床一线抗肿瘤用药, 但抗肿瘤抗生素普遍存在水溶性低、稳定性差和全身毒副作用大等问题。选择合适的递送载体设计合理的递送系统尤其是智能递送系统, 可以提高药物的靶向性和疗效, 降低药物的不良反应。本文对抗肿瘤抗生素递送的载体及递送系统的研究进展进行了综述, 包括现已上市的抗肿瘤抗生素药物制剂、处于临床研究阶段的抗肿瘤抗生素药物制剂和处于基础研究阶段的新型抗肿瘤抗生素药物制剂。

关键词: 抗肿瘤抗生素; 药物载体; 智能递送系统; 靶向性

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Recent advances in the drug formulations of anti-tumor antibiotics

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Abstract: Anti-tumor antibiotics exhibit great application potential in the anti-tumor therapy. Some drugs have become the first-line medication clinically. However, there are always various problems associated with anti-tumor antibiotics, such as poor solubility and instability as well as severe systemic side effects. It is important to choose suitable delivery carriers for a reasonable delivery system for a good targeting ability, enhanced anti-tumor efficacy and reduced adverse effects of the anti-tumor antibiotics, especially in the smart delivery systems. This review summarizes the carriers and the advances in the delivery systems of anti-tumor antibiotics, including anti-tumor antibiotic drugs currently on the market, in the clinical research stage and in the basic research stage.

Key words: anti-tumor antibiotics; drug carrier; smart delivery system; targeting ability

抗肿瘤抗生素是一类由微生物产生的具有抗肿瘤活性的化学物质[1]。放线菌素 D 是第一个被应用在临床上的抗肿瘤抗生素, 用于治疗儿童肾母细胞瘤[2]。抗肿瘤抗生素因其较强的抗肿瘤活性、较宽的抗肿瘤谱, 以及丰富的来源等优点在抗肿瘤研究中扮演着重要的角色。目前, 随着对抗肿瘤抗生素的深入研究, 更多新型的抗肿瘤抗生素被开发成产品, 一些已经跻身为临床一线用药, 如多柔比星 (doxorubicin, DOX) 和柔红霉素 (daunorubicin, DNR) 等。目前常用的抗肿瘤抗生素有烯二炔类、糖肽类、蒽环类、大环内酯类、苯并二吡咯类和苯醌类等几大类, 以力达霉素 (lidamycin, LDM)、卡奇霉素 (calicheamicin)、博来霉素 (bleomycin, BLM)、DOX、雷帕霉素 (rapamycin, Rapa)、丝裂霉素 C (mitomycin C, MMC) 等为代表[1, 2]。一些抗真菌类抗生素药物在近些年也被发现具有抗肿瘤作用, 伊曲康唑 (itraconazole,

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ITN) 通过 Hedgehog 传导通路抑制血管生成从而具有抗肿瘤作用[3]; 著名的抗真菌药物涕必灵 (thiabendazole) 也显示出一定的抗肿瘤潜力, Zhang 等[4]通过细胞实验和体内实验证明了涕必灵可以通过抑制血管内皮生长因子 (vascular endothelial growth factor, VEGF) 而发挥抗黑色素瘤的功效。

然而, 在诸多发现的抗肿瘤抗生素中, 只有少部分进入临床Ⅱ期, 极少部分获批上市。阻碍抗肿瘤抗生素发展的主要原因有: ① 药物的非特异性带来的强毒副作用, 如蒽环类抗生素可引起心脏毒副作用, 博来霉素类可造成肺纤维化, 大环内酯类可产生红细胞毒性等[5−7]; ② 一些药物的强疏水性限制了其在体内的溶解、吸收, 如 Rapa, DNR 等[8, 9]; ③ 由于结构特点, 大部分药物在体内循环时间较短, 且有效剂量范围窄, 需要多次间隔给药[10−12]; ④ 肿瘤多药耐药性的产生[13−15]。药物递送系统 (drug delivery system, DDS) 能够有效地提高药物的药理活性并减少毒副作用的产生[16], 新型药物递送系统的发展加快了新药上市的步伐, 设计抗肿瘤抗生素的新型 DDS 以解决上述问题, 充分发挥该类药物的药效, 降低药物的毒副作用, 成为研究热点之一。本文对已上市的、进入临床研究的和处在基础研究阶段的抗肿瘤抗生素递送策略进行了综述, 主要介绍了新型抗肿瘤抗生素药物制剂的研究和应用, 包括偶联物、脂质体、胶束、树状大分子、凝胶、无机纳米粒和微泡等。

1 已上市的抗肿瘤抗生素药物制剂

Doxil 是目前被 FDA 批准上市的抗肿瘤抗生素制剂中比较有代表性的一类多柔比星脂质体制剂, 1995 年于美国获批上市, 主要用于治疗复发性卵巢癌和转移性乳腺癌, Doxil 的载体材料组成有二硬脂酰基磷脂酰乙醇胺 (DSPE)-聚乙二醇 (PEG)/氢化大豆磷脂 (HSPC)/胆固醇 (Chol), 脂质体的粒径在 80～90 nm。相较 DOX 盐酸盐注射剂, 该制剂对心脏和骨髓的毒副作用有所缓解, 但是随着 Doxil 的使用, 患者会出现一种与补体系统激活相关的假性过敏现象 (CARPA), 这种不良反应可以通过减慢药物滴注速度克服。其他抗肿瘤抗生素如 DNR、Rapa 等也有相关药物制剂获批上市[7]。

除了脂质体, 单抗偶联物和聚合物偶联物等新剂型也推动着抗肿瘤抗生素加快进入市场的步伐。表 1[7, 17−21]为近 30 年部分获批上市的抗肿瘤抗生素药物制剂。

2 处于临床阶段的新型抗肿瘤抗生素药物制剂

随着新载体、新思路的应用, 许多抗肿瘤抗生素药物制剂已经进入临床试验。这些进入临床的递送系统也逐渐趋于智能化, 如 DOX 热敏感脂质体 ThermoDOX[7]、DOX pH 敏感前药 INNO-206[22−24] Ⅲ期临床试验; MMC pH 敏感前药进入Ⅰ期临床试验等[25]。其中, INNO-206 是第一个进入临床、利用体内白蛋白作为运输载体的药物, DOX 与 6-马来酰亚胺己酸通过 pH 敏感腙键连接, 静脉注射进入体循

Table 1 Anti-tumor antibiotic drugs that have been approved in the last 30 years. PEG: Polyethylene glycol; DOX: Doxorubicin; MMAE: Monomethyl auristatin E; DNR: Daunorubicin; Rapa: Rapamycin

Name	Preparation type	Indication	Company, approved time	Main drug	Ref.
Myocet	Non-PEG liposome injection	Breast cancer	Elan, 2000	DOX	[7, 17]
Doxil	PEG liposome injection	Breast cancer, ovarian cancer, multiple myeloma, kaposi's sarcoma	Janssen Res and Dev, 1995	DOX	[7, 17, 18]
Adcetris	Butuxima- MMAE antibody conjugate injection	Hodgkin lymphoma, non-Hodgkin lymphoma, T-cell lymphoma	Seattle Genetics, 2011	MMAE	[18, 19]
Afinitor	Tablet	Advanced renal cancer,breast cancer, lung cancer, pancreatic cancer, gastrointestinal cancer	Norvatis, 2009	Everolimus	[18, 20]
DaunoXome	Clitric acid le erythromycin liposome injection	HIV-associated koposi's sarcoma	Galen (UK), 1996	DNR	[17, 18]
Zinostatin sitalamer	Polymer conjugate injection	Liver cancer	–	Neocarzinostatin	[17]
VYXEOS	Cytarabine: DNR (molar ratio 5∶1) liposome injection	Acute myelogenous leukemia	Celator Pharms, 2017	Cytarabine, DNR	[18, 21]
Erythromycin hydrochloride injection	Injection	Acute myeloblastic leukemia, acute lymphocytic leukemia	West ward Pharms Int, 1998	DNR	[18]
Torisel	Injection	Advanced renal cell carcinoma	PF Prism CV, 2007	Rapa	[18]
Mitoxantrone hydrochloride injection	Injection	Pancreatic cancer	West ward Pharms Int, 2006	Mitoxantrone	[18]
Ellence	Injection	Lymph node positive early breast cancer, advanced or recidivity breast cancer	Pfizer Inc, 1999	Epirubicin	[18]

环后, INNO-206 与循环白蛋白的 34 位半胱氨酸结合, 从而加速药物进入实体瘤并提高药物在实体瘤的聚集, 进入肿瘤组织后, 腙键断裂从而释放出 DOX[22, 24]。表 2[3, 7, 19, 22−34]为近年来进入临床研究的抗肿瘤抗生素药物制剂。

3　处于基础研究阶段的新型抗肿瘤抗生素药物制剂

3.1　药物偶联物

3.1.1　聚合物−药物偶联物　从第一个聚合物−药物偶联物莫斯卡灵−二肽−聚乙烯吡咯烷酮 (PVP) 诞生到现在, 聚合物−药物偶联物已经发展了 60 余年。区别于其他载药系统, 聚合物−药物偶联物中药物和聚合物以共价键的方式连接而非由聚合物包载药物。这种载药形式具有以下优点: ① 增加疏水性药物的水溶性; ② 可以依据不同目的灵活调整共价键类型, 实现在特定环境下药物的释放, 如 pH 敏感键、酶敏感键和光敏感键等; ③ 将药物与聚合物连接显著延长药物在体内循环半衰期; ④ 提高药物的实体瘤的通透和滞留效应 (enhanced permeability and retention effect, EPR)。因此, 这类载体能够克服抗肿瘤抗生素选择性差、稳定性差以及部分药物水溶性差的问题。常用的聚合物有多糖类、PEG、聚氨基酸和多肽等[35]。

为了解决 DOX 因靶向性差带来的心脏毒性, 提高 DOX 在靶组织的分布浓度而提高肿瘤抑制效果, Tu 等[36]设计了一种基质金属蛋白酶 2 (MMP2) 敏感的二肽键聚合物−药物偶联物, 先将 PEG 和细胞穿膜肽 (TAT) 通过 MMP2 敏感二肽连接制得 PEG-ppTAT, 再将 TAT 半胱氨酸残基的巯基与马来酰胺键合的 DOX 连接制得聚合物偶联物 PEG-ppTAT-DOX/MMP2。这种偶联物能够在水溶液中自组装, 具有酶敏感特性而起到靶向效果, 相较于 MMP2 非敏感的聚合物, 该聚合物在 A549 细胞上的转染效率高出 1 倍; 高表达 P-糖蛋白 (P-gp) 的细胞对于 PEG-ppTAT-DOX/MMP2 的药物摄取能力比游离 DOX 高 2 倍, 提示该偶联物能够逆转细胞的耐药性。基因药物与化学药物的共载能够通过发挥协同作用提高肿瘤抑制效果。Lu 等[37]将 β-环糊精 (β-CD) 与聚乙烯亚酰胺 600 (PEI_{600}) 连接制得的二嵌段共聚物 poly-conjugate (PC) 与 DOX 共价结合形成偶联物, 带正电荷的 PEI 可以通过静电作用固缩 p53 质粒, 该复合物体系 PC-DOX/p53 进入细胞后能够借助内涵体逃逸释放药物进入细胞核, 协同诱导细胞凋亡。体内生存率实验结果表明, 游离 DOX 组于给药 24 天后出现 60% 死亡率, 而 PC-DOX/p53 组在给药 45 天后荷瘤小鼠存活率为 60%, 证明以 PEI 为载体共载 p53 质粒和 DOX 的偶联物在抑制肿瘤生长和提高生存期上有着一定优势。

3.1.2　单抗−药物偶联物　单抗−药物偶联物 (antibody-drug conjugates, ADC) 由单抗、药物和连接键三部分元件组成。其中, 单抗发挥靶向作用, 药物发挥细胞毒作用, 当给药系统进入靶部位时, 需要足够量的药物释放出来, 因此, 连接键的选择对于 ADC 的稳定性与释药性能至关重要。连接键主要分为两大类: ① 可断裂的连接键, 化学键在溶酶体酶、酸性刺激和谷胱甘肽 (GSH) 还原下断裂; ② 不可断裂的连接键, 药物的释放主要依赖于单抗在特定部位的降解[19]。

Xu 等[38]以 LDM 为模型药物, 基于 EGFR 和 MMP2 设计了一种双靶向型单抗偶联物。LDM 由可拆分的发色团 (AE) 和蛋白辅基 (LDP) 组成。将靶向 EFGR 的寡核苷酸 Ec 和靶向 MMP2 的单抗 TIMP-2 与 LDP 通过 $(GlyGlyGlyGlySer)_2$ 连接起来, 形成融合蛋白, 最后装配 AE, 最终制得的单抗−药物偶联物对非小细胞型肺癌有着较好的疗效。与游离 LDM 相比, 单抗偶联物对 H460、A549 的细胞毒作用更大 [IC_{50}: H460: 4.05×10^{-11} mol·L^{-1} (游离 LDM), 5.24×10^{-12} mol·L^{-1} (单抗偶联物); A549: 6.67×10^{-10} mol·L^{-1} (游离 LDM), 4.69×10^{-11} mol·L^{-1} (单抗偶联物)], 同时对 H460 异种种植的小鼠抑瘤率更高 (0.2 mg·kg^{-1} 游离 LDM: 55%; 0.2 mg·kg^{-1} 单抗偶联物: 74%)。Yang 等[39]制备了一种结构简单的传统单抗偶联物, 旨在提高 DOX 的体内循环时间、解决 DOX 靶向性差而对靶组织毒性降低的问题, 结构修饰的 DOX 与免疫球蛋白 G (IgG) 共价连接, 通过对 IgG 进行叶酸 (FA)-PEG 修饰, 可以得到靶向 FA 受体的长循环载药系统。相较于无 PEG 修饰的载体, 该偶联物在体内的循环时间多两倍, 与无 FA 修饰的单抗偶联物相比, 该偶联物对 HeLa、KB 细胞的细胞毒作用高 8 倍, 因此 FA-PEG-IgG-DOX 可以作为一种 ADC 给药策略。

3.2　脂质体

脂质体作为一种纳米级别的递送载体, 由于其膜材良好的生物相容性和低毒性以及表面可修饰性, 能够显著提高药物疗效并减少药物对正常组织的毒副作用, 被广泛地应用于药物制剂研究[40, 41]。然而脂质体存在着稳定性低、药物释放缓慢和肝脏/脾脏易聚集等缺陷[41], 因此, 长循环靶向型、环境敏感型脂质体是目前开发热点。肿瘤细胞内富含 GSH, 这为环境响应释药型递送载体提供了设计前提[42]。基于此, Patil 等[43]设计了一种 FA 受体靶向还原响应型脂质体, 许多肿瘤细胞表面高表达 FA 受体, 尤其是上皮细胞,

Table 2 Antitumor antibiotics in the clinical studies. MMC: Mitomycin C; 17-AAG: 17-Allyl amino-17-dimethoxy-gridamycin

Drug	Preparation type	Clinical phase	Indication	Ref.
MMC	pH sensitive lipid prodrug/liposome	Phase Ⅰ	Metastatic colorectal cancer	[25]
Clarithromycin/PF-06647263	Antibody conjugate	Phase Ⅰ	Advanced solid tumor	[26]
17-AAG/AB-010	Albumin nanoparticles	Phase Ⅰ	Solid tumor	[27]
Epirubicin/NC6300	Micelle	Phase Ⅰ	Advanced or metastatic solid tumor	[28]
DOX/AEZS-1-08	Prodrug	Phase Ⅱ	Prostate cancer	[29]
Rapa/ABI-009	Albumin nanoparticles	Phase Ⅱ	Non-muscular infiltrating bladder cancer	[30]
DOX/NK-911	Micelle	Phase Ⅱ	Metastatic pancreatic cancer	[28]
Ansamysin/*L*-annamycin	Liposome	Phase Ⅱ	Breast cancer, acute lymphoblastoma, leukemia	[27]
Mitoxantrone	Polymer nanoparticles	Phase Ⅱ	Liver cancer	[27]
DOX/PK-1	Polymer-drug conjugate	Phase Ⅱ	Breast cancer, lung cancer, colorectal cancer	[31]
MMAE	Antibody conjugate	Phase Ⅱ	Metastatic pancreatic cancer	[26]
DOX/IMMU-120	Antibody conjugate	Phase Ⅱ	Multiple myeloma	[19]
DOX/INNO-206, aldoxorubicin	pH sensitive prodrug	Phase Ⅱ, Phase Ⅲ	Advanced pancreatic duct carcinoma, metastatic and advanced soft tissue sarcoma	[22−24]
Itraconazole	Oral prescriptions, liquid preparations, capsule	Phase Ⅱ Phase Ⅲ	Basal cell carcinoma, non-squamous cell lung cancer, prostate cancer Ovarian cancer	[3, 32, 33]
DOX/ThermoDOX	Thermosensitive liposome	Phase Ⅱ Phase Ⅲ	Breast cancer Liver cancer	[7, 34]
DOX/BA-003	Polymer	Phase Ⅲ	Advanced liver cancer	[27]
DOX/SP1049C	Polymer micelle	Phase Ⅲ	Adenocarcinoma of the esophagus	[7]
Clarithromycin/CMC-544	Antibody conjugate	Phase Ⅲ	Acute myeloid leukemia, non-Hodgkin lymphoma	[19]

FA 作为靶头具有分子质量小、无毒、无免疫原性和受体亲和力强等优点，作者将 MMC 与脂质通过二硫键连接形成 MMC 前药实现还原响应。以该脂质体复合物为载体递送 MMC 能够提高 MMC 的半衰期并显著增加 MMC 的肿瘤靶向性，该系统有望提高 MMC 治疗腹膜癌扩散及浅表性膀胱癌的能力。Liu 等[44]基于肿瘤组织的缺氧环境特点研究了一种治疗脑胶质瘤的、由硝基咪唑类组成的载 DOX 缺氧敏感型脂质体，硝基咪唑在缺氧条件下转变为氨基咪唑从而释放药物发挥治疗作用。硝基咪唑递送系统能够提高 DOX 穿过血脑屏障的效率，并减少脑胶质瘤因其生理结构而产生的易抗药性。硝基咪唑对辐射敏感，研究者以此思路将化疗与放疗结合起来，对荷脑胶质瘤的小鼠进行生存期实验，结果表明缺氧敏感型脂质体相较于游离 DOX 来说能够延长小鼠生存周期 (缺氧敏感型脂质体: 47 天；游离 DOX: 44.5 天)，而结合辐射治疗后，生存周期进一步延长到 65.5 天。此外，由 Fe_3O_4 组成的磁性脂质体也成为一类具有潜力的载体。Wang 等[45]用聚乳酸聚乙醇酸共聚物 (PLGA)、Fe_3O_4 和聚谷氨酸等设计了一种载多柔比星的磁性脂质体−壳核纳米球 PLGA/多功能聚合物脂质体 (multifunctional polymer liposomes, MPLs)，将 RGD 和 TAT 修饰在表面分别起靶向和穿膜作用，RGD 是一段靶向肿瘤新生血管表面 $\alpha v\beta 3$ 和 $\alpha v\beta 5$ 凝集素的三肽 (Arg-Gly-Asp)[46]，该递送系统同时实现了化学药物与基因药物的共载，提高了 DOX 的脑靶向性，相较于单修饰组和无 Fe_3O_4 装载组，PLGA/MPLs 组对胶质瘤的疗效有所提高。与表面单修饰的 PLGA/PL-RGD 与 PLGA/PL-TAT 组相比，PLGA/MPL 组在 C6 细胞上的摄取转染率相对较高，提示多功能脂质体能够提高细胞对药物的摄取能力。

3.3 胶束

将双亲性的高分子聚合物分散在水中，当浓度超过临界胶束浓度 (critical micelle concentration, CMC) 可以自组装形成胶束，粒径在 10～100 nm，以胶束作为药物的载体可以提高 EPR 效应，对胶束表面进行修饰后，亦可以实现主动靶向作用，继而减少胶束递送系统与无关组织的作用。根据药物的性质不同，将会被装载在胶束的不同位置处：疏水性药物倾向于聚集在疏水性内核，而亲水性药物在亲水性外壳中。药物和胶束的结合方式多样，包括疏水作用力、共价键和交联作用[47, 48]。

黏蛋白 1 (MUC1) 受体是一类由两个亚单元组成的高表达于肿瘤细胞表面的异源二聚体蛋白，是肿瘤治疗的一个重要靶点。为了提高 DOX 在乳腺癌组织的浓度，并减少 DOX 用量，Charbgoo 等[49]设计了一种基于 MUCI 适配体的靶向性 DNA 胶束 DOX-KLA 肽-anti MUCI-M。他们将胆甾醇基修饰的 MUC1

适配体单链 DNA 和由促凋亡 KLA 阳离子肽修饰的双链 DNA 混合, 在水溶液中自组装成混合胶束, 实现对 DOX 和 KLA 的共载, DOX 和 KLA 肽共递送能够减少 DOX 用量, 减轻其毒副作用。这种靶向胶束在体外的释放行为和体内的抗肿瘤活性都显示出较好的结果。游离 DOX 与该胶束对高表达 MUCI 的 MCF-7 细胞 IC_{50} 值分别为 2.5 和 1 μmol·L^{-1}; DOX-MUCI-M、KLA-anti MUCI-M、DOX-KLA-anti MUC1-M 对 MCF-7 细胞的凋亡及坏死诱导率分别为 18.5%、23.6% 和 28.3%, 这说明建立的 DNA 胶束对高表达 MUCI 蛋白的癌细胞抑制效果更好; 对荷 C26 肿瘤的小鼠静脉注射相同浓度 (5 mg·kg^{-1}) 的游离 DOX 和 DNA 胶束观察药物体内抗肿瘤效果, 以瘤体积小于 2 cm^3 为标准, DOX 组于 26 天有 2/3 小鼠死亡, 而 DNA 胶束组在治疗的 30 天中小鼠都存活并达到了治疗标准, 提示新设计的胶束提高了抗肿瘤效果。非离子型表面活性剂 Pluronic 也被应用到了胶束制备中, Li 等[50]将 Pluronic F68 与高分子材料 PEG、聚己内酯 (PCL) 和 PLGA 混合形成聚合物混合胶束装载米托蒽醌, 这类胶束能够通过光敏剂提高激活活性氧 (ROS) 的水平, 利用光动力治疗克服乳腺癌对米托蒽醌等药物的多药耐药性。在体外耐药性 MCF-7 细胞毒实验中, 有光刺激时, 相同浓度 (20 μmol·L^{-1}) 的游离米托蒽醌组和胶束组对细胞生存抑制率分别为 11% 和 60%; 撤去光刺激后, 胶束组的细胞生存抑制率降低至 43%, 这些结果表明胶束在结合光刺激时可以发挥最大的肿瘤抑制能力。

普通胶束在体内存在着循环稳定性差或在病理部位释药慢的问题, 研究环境响应型胶束对于提高胶束的循环稳定性及智能释药性有着重要意义[51, 52]。Quader 等[46]将表柔比星和聚合物胶束材料聚乙二醇-*b*-聚-*β*-苄基天冬酰胺 (PEG-*b*-PBLA-Ac) 共聚物通过酸敏感腙键连接, 并对胶束表面进行 cRGD 修饰, 继而制备载表柔比星的靶向性酸敏感聚合物胶束, 研究表明, 该递送系统具有极强的深入恶性肿瘤 (如脑胶质瘤) 组织的能力; 该 pH 敏感胶束能够通过提高表柔比星的脑靶向性解决表柔比星血脑屏障透过效率低的问题。值得一提的是, Maiti 等[13]设计了一种简单但智能的还原环境响应型胶束 [聚乙二醇-*b*-聚 2-甲基丙烯酰氧基乙基, 5-(1,2-二硫-3-基) 戊酸] (PEG-*b*-PLAHEMA), 该嵌段共聚物上的 LAHEMA 部分可以对还原剂 GSH 做出响应而发生结构变化以提高药物的肿瘤靶向性, DOX 和维拉帕米作为模型药物装载在胶束中。孵育 24 h 后, 一种该智能双载胶束 BCP23CCM 对产生多药耐药性的 MDA-MB-231 细胞的 IC_{50} 为 0.959 2 μmol·L^{-1}, 远低于单载 DOX 胶束 BCP23CCM (2.9 μmol·L^{-1}) 和游离 DOX (14.75 μmol·L^{-1})。这提示, 维拉帕米作为一种 P-gp 抑制剂, 与 DOX 的共载能够通过克服 DOX 的耐药性, 减少药物的外排而提高药效。

3.4　树状大分子

聚酰胺 (PAMAM) 是一类低毒, 无免疫原性的阳离子高分子材料, PAMAM 树状大分子在递送基因药物和化学药物上都显示一定的潜力。其材料正电荷赋予递送系统质子海绵效应, 继而发挥溶酶体逃逸功能[53, 54]。然而, PAMAM 表面高度正电荷会产生细胞毒性而阻碍其使用, Han 等[53]将透明质酸 (HA) 包载于 PAMAM 表面, 一方面中和了一部分正电荷; 另一方面对 CD44 高表达的细胞具有靶向作用, 共载 DOX 和靶向主要穹窿蛋白 (MVP) 的 siRNA。PAMAM-HA 组对耐药 MCF-7 细胞的 IC_{50} 值为 11.3 μmol·L^{-1}, 远低于游离 DOX 的 IC_{50} 值 48.5 μmol·L^{-1}; 同时, PAMAM-HA 组的体内生物利用度 (4.79 h·μg·mL^{-1}) 和平均滞留时间 (21.8 h) 高于 PAMAM 组 (0.98 h·μg·mL^{-1}, 3.1 h); 而 HA 修饰的树状大分子会提高 siRNA 的细胞转染效率。上述结果表明, 该树状大分子对 DOX 耐受的 MCF-7 细胞具有耐受逆转作用, 是一个非常有效的、用于化学药物和基因药物共载的载体。

除了 PAMAM 树状大分子, 基于 DNA 的树状大分子也有良好的载药能力。Taghdisi 等[55]设计了一种以三磷酸腺苷 (ATP) 适配体为树状大分子构建块, 连接 MUCI 适配体和 AS1411 适配体的载表柔比星双靶向型 DNA 树状大分子, 以解决表柔比星靶向性差的问题, 该载体在富含 ATP 的溶酶体环境中裂解释放出药物。DNA 树状大分子具有良好的稳定性、单层分散性和多孔性等优点。

3.5　凝胶

纳米凝胶作为一种载体, 相较于其他传统载体, 具有更好的生物相容性、更高的载药空间、更强的稳定性及更有效的细胞摄取效率等优点[56]。在特定的环境下 (如 pH 变化、酶降解等) 纳米凝胶会吸水膨胀, 缓慢释放药物[57]。Wang 等[57]基于 PAMAM 树状大分子设计了一种装载 DOX 的交联纳米凝胶, 在 PAMAM 表面修饰生物黏附短肽和酶敏感肽, PAMAM 的树枝在 $NaIO_4$ 的作用下发生交联形成酶敏感的纳米凝胶。该体系对肿瘤组织中高表达的中性粒细胞弹性蛋白酶敏感, 能够提高 DOX 的稳定性、穿过血脑屏障的效率及肿瘤靶向效率。

原位凝胶具有在低温下呈流动状，在胶凝转变温度以上时黏度增加形成半固体状物质的特点。因此，原位凝胶具有在体内形成药物储库缓慢释放药物的能力。为了减轻 BLM A6 在使用中因半衰期短、清除率高而多次重复、大剂量给药产生的毒副作用，Ding 等[11]采用 Pluronic F127 为基质，与包载 BLM A6 的阴离子脂质体共同形成原位凝胶。研究表明，Pluronic F127 是一类重要的温敏型胶体，阴离子磷脂二棕榈酰磷脂酰甘油 (DPPG) 的加入可以提高凝胶间的凝胶强度，从而增加原位凝胶的稳定性，减少药物的泄露。该递送系统将 Pluronic F127 的温敏性质和脂质体的缓释能力结合起来，体外释放结果表明，在阴离子脂质体原位凝胶系统、原位凝胶系统和 BLM A6 溶液中，阴离子脂质体原位凝胶系统的释药速度最慢，在 4 h 时释放 51%，远低于原位凝胶系统 (78%) 和 BLM A6 溶液 (90%)，在 48 h 时，阴离子脂质体凝胶递送系统释放了 83% BLM A6，其余二者均几乎完全释药；体内滞留实验表明，阴离子脂质体原位凝胶系统在注射部位的滞留时间远长于 BLM A6 溶液，可以监测到注射 7 天后，而 BLM A6 溶液在注射 24 h 后注射部位已经检测不到药物信号。

3.6 无机材料纳米粒

金纳米粒、多孔硅纳米粒、Fe_3O_4 磁性纳米粒和碳纳米管等含无机材料的纳米递送系统因材料对化学物质和高温的强耐受性、高载药能力、内外表面易修饰性和体外低毒性[58, 59]等优点，被广泛应用于药物递送载体的研究中。Yang 等[60]设计了一种基于多能干细胞 (iPS) 的装载 MMC 的靶向型金纳米粒 CXCR4-AuNP/SiO_2。iPS 具有较好的肿瘤倾向性，将化学药物装入 iPS 内可以提高其在肿瘤部位的聚集。但 iPS 在肝脏、肾脏、脾脏和肺等组织的聚集会产生畸形瘤继而阻止 iPS 的临床应用，而 DOX 能够压制 iPS 的浸润迁移，从而解决该问题。CXCR4 是一类表达于 iPS 表面具有靶向肿瘤细胞基质细胞衍生因子 1 (SDF1) 受体功能的蛋白。他们在过去的研究中提出将 CXCR4 连接在 AuNP/SiO_2 表面能够增加 iPS 对纳米粒的摄取[61]。同时，金纳米粒具有对光刺激敏感并将光刺激转换为热能的性质，能够应用到光动力治疗中。给予光刺激后，体内生存率实验表明，相较于游离的 MMC，AuNP/SiO_2 和 MMC-CXCR4-AuNP/SiO_2 治疗组的荷瘤小鼠生存周期更长 (三者分别为 5、8 和 10 天)。Meng 等[62]用 PEI-PEG 共聚物修饰多孔硅纳米粒，共载 DOX 和靶向 P-gp 的 siRNA，在治疗乳腺癌上发挥着协同作用，siRNA 在靶部位可以定向下调 P-gp 的表达而减少化学药物的排出，诱导细胞凋亡的能力有所提高。多孔硅纳米粒作为一种新型的载体，具有粒径孔径可控性，降解产物无毒副作用[59]等特点，可以对药物起到控释和靶向作用。

3.7 超声微泡

超声微泡是一类由白蛋白、碳水化合物或脂质组成的壳包围着气体内核 (通常是空气、氮气或全氟化碳) 组成的药物递送载体，已经被用作超声造影剂和血液流动示踪剂[63]。超声微泡作为药物载体，被注射到体内后，在靶组织给予一定强度的超声照射，微泡将破裂释放出药物，可以显著促进药物吸收，提高药效。超声微泡作为一种新型的药物定位释放载体，为疾病治疗提供了无创、简便和高效的新方法[64]。

Chapius 等[63]以 BLM A5 生物素-PEG 共聚物为材料制备了超声微泡。超声微泡以共聚物为外壳，生物素和 PEG 作为基本骨架，共价结合模型药物。在 MCF-7 体外模型中观察到微泡能够黏附在细胞表面，提示该微泡具有细胞黏附选择性。Luo 等[65]设计了一种装载 pH 敏感且双靶向型 DOX 前药的微泡递送系统，DOX 与琥珀酸肝素通过 pH 敏感腙键连接，表面修饰 FA 靶头和 cRGD 靶头，以生物素作为微泡壳的基本材料，制备前药−微泡复合物 (DPMC)。该递送系统能够提高 DOX 的肿瘤靶向性，相较于游离的 DOX 和 DOX 前药，DPMC 对 MCF-7 细胞的细胞毒作用更强 (IC_{50} 分别为 310.35、217.43 和 120.23 ng·mL^{-1})；体内实验中，结合超声照射后 DPMC 组瘤重量显著低于 PBS 组、游离 DOX 组和 DMPC 组。上述结果说明，结合超声微泡与酸敏感靶向型前药的治疗策略具有一定的优越性。

3.8 其他纳米粒

由阳离子载体形成的纳米粒可以提高药物跨膜效率，同时也能实现化学药物和基因药物的共载。Chang 等[66]将米托蒽醌和在生理条件下带正电荷的十六碳烯酸共价结合成二米托蒽醌和单米托蒽醌产物，二者以 1∶1 摩尔比混合形成阳离子纳米粒，同时用以固缩靶向髓细胞白血病 1 基因 (Mcl-1) 的 siRNA (siMcl-1)，Mcl-1 是 Bcl-2 家族中的重要成员，具有抵御凋亡的能力，因此通过下调 Mcl-1 的表达可以减弱肿瘤细胞的耐药性及增加肿瘤细胞对化学药物的敏感性而更好地抑制肿瘤发展。共载策略能够克服肿瘤对米托蒽醌等多药耐药性，阳离子载体提高了药物进入细胞的能力，并依托其提高的靶向性减少化学药物的用量、减轻毒副作用，该纳米粒表现出很强抑制肿瘤生长的能力，当荷瘤小鼠给药 20 天后，共载

纳米粒组相较于未治疗组的肿瘤抑制率增加了 83.4%, 而游离米托蒽醌组相较于未治疗组的肿瘤抑制率增加 55.4%。Taghavi 等[67]用 PLGA、壳聚糖 (CS) 为材料制备了阳离子纳米粒, 通过在纳米粒表面修饰 5TR1 DNA 适配体实现对 MUCI 受体的靶向功能, 制得包载表柔比星的 5TR1 aptamer-CS-PLGA 靶向型阳离子纳米粒。相较于非靶向性型和游离型药物, 该靶向纳米粒在 C26 结肠癌小鼠体内实验中表现出了更好的肿瘤抑制作用。

聚合物脂质纳米粒是一类由脂质内核和聚合物外壳组成的壳−核结构, 同时具有脂质体和纳米粒的理化特征, 因而具有更好的生物相容性和稳定性[68]。基于此, Li 等[12]设计了一种由 FA 作为靶头, 以 MMC 的磷脂复合物为内核, PEG-DSPE 作为外壳形成的聚合物脂质纳米粒, 磷脂复合物作为 MMC 的一种前药形式, 大豆油与药物通过静电作用、氢键和范德华力结合成对 pH 敏感的大豆油磷脂酰胆碱复合物 (SPC)。该纳米粒有以下优点: ① 极好地解决了强亲水的 MMC 的纳米粒包封问题; ②通过靶向作用提高了药物在肿瘤部位的聚集; ③ SPC 的 pH 敏感性进一步增加了药物在肿瘤部位的浓度; ④ PEG 修饰可以实现长循环功能。

近年来, 在研的载抗肿瘤抗生素的聚合物−药物偶联物递送系统、部分新型抗肿瘤抗生素脂质体递送系统和其他处于基础研究阶段的纳米粒总结于表 3[8, 9, 11−13, 36−39, 43−46, 49, 50, 53−60, 62, 63, 65−67, 69−102]。

4　展望

抗肿瘤抗生素作为一类化疗药物, 在多年的研究与临床应用中显示出较强的抗肿瘤活性和较宽的抗肿瘤谱。随着多种递送载体的发展, 抗肿瘤抗生素各种剂型的合理应用可以在一定程度上克服其固有缺陷, 如药物溶解性差、选择性低、毒性高和半衰期

Table 3　New antitumor antibiotic drugs in the basic research stage.　HA: Hyaluronic acid; *β*-CD: *β*-Cyclodextrin; ITA: Itraconazolel; PEI: Poly(ethyleneimine); RGD: Arg-Gly-Asp; AHGDM: Aminohexylgeldanamycin; HPMA: *N*-(2-Hydroxypropyl) methacrylamide; Glut: Glutaric acid; Lys: Lysine; Gly: Glycine; ppTAT: Matrix metalloproteinase (MMP2)-cleavable cell penetrating peptide; SMCC: Succinimidyl-4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate; Bcl: B-cell lymphoma; ODN: Oligonucleotide; cAC10-SGGPEGGS: Anti CD30 antibody-serine-(glycine)$_2$-proline-glutamic acid-(glycine)$_2$-serine; LDM: Lidamycin; EGFR: Epidermal growth factor receptor; TIMP-2: Tissue inhibitor of metalloproteases; FA: Folic acid; NGR: Asparagine-glycine-arginine; DSPE: Distearoyl phosphoethanolamine; PC: Phosphocholine; ICG-ODA: A hydrophobically modified photosensitizer; Her2: Human epidermal growth factor receptor 2; $H_7K(R_2)_2$: (Arginine)$_2$-(histidine)$_7$-methionine-(arginine)$_2$ peptide; DOPE: Dioleoyl phosphoethanolamine; TAT: Tyrosine-glycine-arginine-(lysine)$_2$-(arginine)$_2$-glutamine-(arginine)$_3$; PLGA: Poly(*D*,*L*-lactide-co-glycolide); GFP: Green fluorescent protein; OQPGA: Octadecyl-quaternized modified poly(*g*-glutamic acid); DPPC: Dipalmitoyl phosphatidylcholine; DSPC: Distearoyl phosphatidylcholine; MBHA: Rink amide *p*-methylbenzhydrylamine; DOPG: Dioleoyl phosphatidylglycerole; CA8: (Cholic acid)$_8$; PBLA: Poly(*β*-benzyl-aspartamide); KLA: (Lysine-leucine-alanine-lysine-leucine-alanine-lysine)$_2$; CS: Chitosan; PCL: Poly(*ε*-caprolactone); PLAHEMA: Poly 2-(methacryloyloxy) ethyl 5-(1, 2-dithiolan-3-yl) pentanoate; TPGS: *D*-*α*-tocopherol polyethylene 1000 succinate; PF: Pluronic F; PLL: Poly (*L*-lysine); PMPC: Poly (methacryloyloxyethyl phosphorylcholine); PLA: Polylactide; VIP: Vasocative intestinal peptide; SPA: Succinimidylpropionate; PAMAM: Poly(amido amine); MVP: Major vault protein; TPP: Sodium tripolyphosphate; BLM: Bleomycin; PECT: Poly(*ε*-caprolactone-co-1,4,8-trioxa [4.6] spiro-9-undecanone)-poly(ethyleneglycol)-poly (*ε*-caprolactone-co-1,4,8-trioxa [4.6] spiro-9-undecanone); DPPG: Dipalmitoyl phospha-tidylglycerol; CXCR4: Chemokine receptor; DC: Dendritic cell; FKBP: FK-506 binding protein 12; ELP: Elastin-like polypeptides; SP: Soybean phosphatidylcholine; LDL: Low density lipoprotein; mdr: Multi-drug resistence

Preparation type	Carrier	Cargo	Characteristic	Cell line	Ref.
Polymer-drug conjugate	HA/3-amino-4-methoxybenzoic acid	Rapa	CD44 targeting	MDA-MB-468	[9]
	Albumin	ITA	−	A549	[69]
	β-CD/PEI_{600}	DOX, p53 plasmid	Cationic co-delivery	MCF-7	[37]
	RGD_{fk}/AHGDM/HPMA	Docetaxel, 17-AAG	Targeting, pH sensitive	A2780	[70]
	Poly-bis-(*ε*-Lys-Glut) PEG-$(Gly)_3$	Rapa	−	PC-3	[71]
	PEG2000-ppTAT-SMCC	DOX	Enzyme sensitive	A549, MCF-7, HT1080	[36]
	HA	DOX, camptothecin	CD44 targeting	4T1	[72]
	Four-arms PEG	DOX, anti-Bcl ODN	pH sensitive, co-delivery	A549	[73]
Antibody-drug conjugate	cAC10-SGGPEGGS	LDM	CD30 targeting	Karpas299, L540, Raji	[74]
	Anti-EGFR ODN Ec/ TIMP-2	LDM	EGFR targeting, enzyme sensitive	H460, A549, A431, KYSE150, HT1080, PANC-1	[38]
	FA-PEG-IgG	DOX	Targeting	HeLa, KB	[39]
	RGD-NGR	C-1027	CD13 targeting	MDA-MB-468, MDA-MB-231, SK-BR-3	[75]

Continued

Preparation type	Carrier	Cargo	Characteristic	Cell line	Ref.
	Proximimab antibody	Duocarmycin	CD56 targeting	NLI-H128, 446, 524, 529, 69	[76]
	Gemtuzumab ozogamicin, inotuzumab ozogamicin	Calicheamicin	pH sensitive	−	[77]
Liposomes	FA, hydrogenated soybean oilphosphatidylcholine, cholesterol, PEG_{2000}-DSPE	MMC-lipid prodrug	Targeting, reduction sensitive	HiFR	[43]
	Her2 antibody, PLsPC, PEG_{2000}-DSPE, PC	DOX, ICG-ODA	Her-2 targeting, light sensitive	MCF-7	[78]
	$H_7K(R_2)_2$, DSPE-PEG, cholesteryl succinate, DOPE	DOX	pH sensitive	C6, U87	[79]
	Nitroimidazole, chelosterol, PEG_{2000}-DSPE	DOX	Hypoxia sensitive	C6, U87	[44]
	TAT, RGD, PLGA, Fe_3O_4, cholesterol, OQPGA, PEG	Epirubicin, GFP gene	Targeting, magnetic liposomes	C6	[45]
	DPPC, DSPC, PEG_{2000}-DSPE, cholesterol	Idarubicin	Thermosensitive	B16BL6, BLM	[80]
	Trastuzumab, cholesteryl succinate, DPPC, DSPE-PEG	Rapa	Photothermal sensitive	BT-474	[81]
	MBHA resin, DOPG, PEG_{2000}-DSPE	Mitoxantrone	−	HeLa	[82]
Micelles	CLL1 aptamer-PEG5000-CA8	DNR	CLL1 targeting	Leukemia stem cells	[8]
	cRGD-PEG-PBLA-Ac	Epirubicin	Targeting, pH sensitive	U87	[46]
	KLA-cholesterol-DNA-anti MUC1 aptamer	DOX, KLA	MUC1 targeting, DNA micelles	MCF-7, CHO	[49]
	PEG-stearic acid -CS	MMC	Targeting, pH sensitive	HepG2	[83]
	mPEG-PCL-*g*-PEI	DOX, pDNA	Co-delivery	L929, HEK293	[84]
	PEG-*b*-PLAHEMA	DOX, verapamil	Reduction sensitive	MDA-MB-231	[13]
	TPGS-s-s-mitoxantrone	Mitoxantrone, TPGS	Reduction sensitive	MDA-MB-231	[85]
	PCL-PF68-PCL/ PLGA-PEG-PLGA	Mitoxantrone	Light sensitive	MCF-7	[50]
	PLL-*b*-PMPC	DOX-carboxymethyl benzaldehyde	pH sensitive	HeLa, 4T1	[86]
	PF123, F127	17-AAG	−	U87	[87]
	PEG-PLA	ITA	−	A549	[69]
	VIP-PEG-DSPE-SPA	17-AAG	Targeting	MCF-7	[88]
Dendrimers	HA-PAMAM	DOX, siRNA (MVP)	CD44 targeting	MCF-7	[53]
	PF68-PAMAM	DOX	−	MCF-7	[54]
	MUC1/AS1411 aptamer-ATP aptamer DNA dendrimers	Epirubicin	MUC1, AS1411 double targeting, pH sensitive	MCF-7, C26, CHO	[55]
	RGD-generation 5 PAMAM	Rapa	Targeting	PC3, C4-2B, MDA-MB-231, HeLa	[89]
	Poly(*L*-lysine) dendrimers/ silsesquioxane cube	DOX, siRNA (luciferase)	EGFR targeting, co-delivery	U87	[90]
Hydrogels	Matrix: Pluronic F127 materials: CS, TPP	BLM	pH sensitive	HaCaT, HDF	[57]
	PECT/HA	DOX, ^{131}I	Thermosensitive *in situ* gel	HepG2	[91]
	Pluronic F127, PC S100, cholesterol, DPPG	BLM A6	Thermosensitive *in situ* gel	−	[11]
	Arginine-(alanine) 2-aspartic acid-*D*-tyrosine-cysteine (RAADyC) and arginie-glycine-aspartic acid-cysteine (RGDC) modified PAMAM/$NaIO_4$ cross linked gel	DOX	pH sensitive	C6	[56]
In-organic nanoparticles	sgc8c-Au	DNR	Targeting, pH sensiive	MoH-4, U266	[58]
	PEI-PEG-PEI/porous silicon	Epirubicin	pH sensitive	C26	[59]
	CXCR4-Au/SiO_2	MMC	Targeting	MGC803	[60]
	DC-SIGN-porous silicon	Rapa	Targeting	Human monocyte derived DC	[92]

Continued

Preparation type	Carrier	Cargo	Characteristic	Cell line	Ref.
	PLGA/Fe_3O_4	17-AAG	Magnetic nanoparticles	MIA Paca-2	[93]
	PEI-PEG-porous silicon	DOX, siRNA (P-gp)	Co-delivery	MCF-7	[62]
Microbubbles	PEG-biotin	Rapa	−	MCF-7	[63]
	FA/cRGD-succinicheparin/biotin	DOX	FA mediated active targeting	MCF-7, A549	[65]
	Anti-ABCG2 antibody-microbubble	Epirubicin	Targeting	MM RPMI 8826	[94]
Other nanoparticles	Cationic hexadecanoic acid	Mitoxantrone, siMcl-1	Co-delivery	KB	[66]
	5TR1 aptamer-CS-PLGA	Epirubicin	Targeting, pH sensitive	MCF-7, CHO	[67]
	Poly(butyl-cyanoacrylate)	Epirubicin	−	HeLa	[95]
	HA-lysine-lipoic acid	DOX	CD44 targeting, reduction sensitive	MCF-7	[96]
	HA/CS	Mitoxantrone, verapamil	CD44 targeting	MCF-7	[97]
	FKBP-ELP fusion protein	Rapa	−	MDA-MB-464	[98]
	FA-mPEG-CS	MMC	Targeting	HeLa	[99]
	FA-PEG-DSPE	MMC-SP phospholipid complex	Targeting, pH sensitive	HeLa	[12]
	β-CD/methyl methacrylate (MMA)-butyl acrylate (tBA)	Idarubicin	pH sensitive	A549, Caco-2	[100]
	N-Succinyl CS-cholesterol-LDL	DOX, siRNA (mdr-1)	Targeting, co-delivery	HepG2	[101, 102]

短等。智能递送系统的发展，使药物具有可控的释药性能，多种递送形式的出现能够让设计者依据药物的特性选用合适的策略以达到疗效最大化。此外，一些载体也赋予化学药物与基因药物共载策略，二者协同作用在一定程度上具有逆转肿瘤耐药性的潜能。然而，任何一个全身给药系统都无法达到将药物全部递送到靶部位，抗肿瘤抗生素制剂的发展仍然要克服许多障碍。现如今，理想的递送载体应该是简单、安全、低毒、稳定和具有高转染效率的；在此基础上，选择恰当的修饰策略并控制药物释放是一个难题；对于共载而言，合适的药物组成及药物比例也是未来需要深入探讨的问题；新型 ADC 策略依然面临着单抗和药物偶联后出现与抗原结合力下降和靶向效果减弱的问题。与此同时，建立一个更有效的体外评估系统用于预测递送系统的体内行为对制剂的发展有着极大的推动作用。相信，未来的研究会更加关注上述问题，重视药物的性质与体内环境特征，充分地发挥抗肿瘤抗生素的潜能。

References

[1] Yang Q. Research progress and clinical application of anti-tumor antibiotics [J]. Tianjin Pharm (天津药学), 2014, 26: 50−53.

[2] Demain AL, Vaishnav P. Natural products for cancer chemotherapy [J]. Microb Biotechnol, 2011, 4: 687−699.

[3] Pounds R, Leonard S, Dawson C, et al. Repurposing itraconazole for the treatment of cancer [J]. Oncol Lett, 2017, 14: 2587−2597.

[4] Zhang J, Zhao C, Gao Y. Thiabendazole, a well-known antifungal drug, exhibits anti-metastatic melanoma B16F10 activity *via* inhibiting VEGF expression and including apoptosis [J]. Pharmzie, 2013, 68: 962−968.

[5] Chen J, Stubbe J. Bleomycins: towards better therapeutics [J]. Nat Rev Cancer, 2005, 5: 102−112.

[6] Eloy JO, Petrilli R, Chesca DL, et al. Anti-HER2 immunoliposomes for co-delivery of paclitaxel and rapamycin for breast cancer therapy [J]. Eur J Pharm Biopharm, 2017, 115: 159−167.

[7] Cagel M, Grotz E, Bernabeu E, et al. Doxorubicin: nanotechnological overviews from bench to bedside [J]. Drug Discov Today, 2017, 22: 270−281.

[8] Zhang H, Li Y, Lin TY, et al. Nanomicelle formulation modifies the pharmacokinetic profiles and cardiac toxicity of daunorubicin [J]. Nanomedicine (Lond), 2014, 9: 1807−1820.

[9] Zhao Y, Zhang T, Duan S, et al. CD44-tropic polymeric nanocarrier for breast cancer targeted rapamycin chemotherapy [J]. Nanomedicine, 2014, 10: 1221−1230.

[10] Liu M, Li W, Larregieu CA, et al. Development of synthetic peptide-modified liposomes with LDL receptor targeting capacity and improved anticancer activity [J]. Mol Pharm, 2014, 11: 2305−2312.

[11] Ding W, Li Y, Hou X, et al. Bleomycin A6-loaded anionic liposomes with *in situ* gel as a new antitumoral drug delivery system [J]. Drug Deliv, 2016, 23: 88−94.

[12] Li Y, Lin J, Yang X, et al. Self-assembled nanoparticles based on amphiphilic anticancer drug-phospholipid complex for targeted drug delivery and intracellular dual-controlled release [J]. ACS Appl Mater Interfaces, 2015, 7: 17573−17581.

[13] Maiti C, Parida S, Kayal S, et al. Redox-responsive core-cross-linked block copolymer micelles for overcoming multidrug resistance in cancer cells [J]. ACS Appl Mater Interfaces, 2018, 10: 5318−5330.

[14] Gazzano E, Rolando B, Chegaev K, et al. Folate-targeted liposomal nitrooxy-doxorubicin: an effective tool against P-glycoprotein-positive and folate receptor-positive tumors [J]. J Control Release, 2018, 270: 37−52.

[15] Katiyar SS, Muntimadugu E, Rafeeqi TA, et al. Co-delivery of rapamycin- and piperine-loaded polymeric nanoparticles for breast cancer treatment [J]. Drug Deliv, 2016, 23: 2608−2616.

[16] Anselmo AC, Mitragotri S. An overview of clinical and commercial impact of drug delivery systems [J]. J Control Release, 2014, 190: 15−28.

[17] Weissig V, Pettinger TK, Murdock N. Nanopharmaceuticals (part 1): products on the market [J]. Int J Nanomed, 2014, 9: 4357−4373.

[18] FDA: FDA approved drug products [EB/OL]. Silver Spring: U.S. Food and Drug Administration, 2018 [2018-03-30]. https://www.fda.gov/drugsatfda.html.

[19] Perez HL, Cardarelli PM, Deshpande S, et al. Antibody-drug conjugates: current status and future directions [J]. Drug Discov Today, 2014, 19: 869−881.

[20] Everolimus [EB/OL]. Bethesda: National Cancer Institute, 2009 [2018-03-30]. https://www.cancer.gov/about-cancer/treatment/drugs/everolimus.html.

[21] Talati C, Lancet J. CPX-351: changing the landscape of treatment for patients with secondary acute myeliod leukemia [J]. Future Oncol, 2018. DOI: 10.2217/fon-2017-0603.

[22] Kratz F, Azab S, Zeisig R, et al. Evaluation of combination therapy schedules of doxorubicin and an acid-sensitive albumin-binding prodrug of doxorubicin in the MIA PaCa-2 pancreatic xenograft model [J]. Int J Pharm, 2013, 441: 499−506.

[23] Kratz F. DOXO-EMCH (INNO-206): the first albumin-binding prodrug of doxorubicin to enter clinical trials [J]. Expert Opin Investig Drugs, 2007, 16: 855−866.

[24] Sachdev E, Sachdev D, Mita M. Aldoxorubicin for the treatment of soft tissue sarcoma [J]. Expert Opin Investig Drugs, 2017, 26: 1175−1179.

[25] Intravenously administered Pegylated liposomal mitomycin C lipid-based prodrug (PROMITIL) in cancer patients with solid tumors [EB/OL]. Bethesda: National Library of Medicine, 2012 [2018-3-30]. https://www.clinicaltrials.gov/ct2/show/NCT01705002?term=mitomycin+c&phase=0&rank=9.html.

[26] Govindan SV, Sharkey RM, Goldenberg DM. Prospects and progress of antibody-drug conjugates in solid tumor therapies [J]. Expert Opin Biol Ther, 2016, 16: 883−893.

[27] Perez-Herrero E, Fernandez-Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy [J]. Eur J Pharm Biopharm, 2015, 93: 52−79.

[28] Cabral H, Kataoka K. Progress of drug-loaded polymeric micelles into clinical studies [J]. J Control Release, 2014, 190: 465−476.

[29] Doxorubicin-GnRH agonist conjugate AEZS-108 in treating patients with metastatic hormone-resistant prostate cancer [EB/OL]. Bethesda: National Library of Medicine, 2010 [2018-03-30]. https://www.clinicaltrials.gov/ct2/show/NCT01240629? term=d.html.

[30] Phase 1/2 study of ABI-009 in nonmuscle invasive bladder cancer [EB/OL]. Bethesda: National Library of Medicine, 2013 [2018-03-30]. https://www. clinicaltrials.gov/ct2/show/NCT02009332?term=ABI-009&rank=3.html.

[31] Seymour LW, Ferry DR, Kerr DJ, et al. Phase II studies of polymer-doxorubicin (PK1, FCE28068) in the treatment of breast, lung and colorectal cancer [J]. Int J Oncol, 2009, 34: 1629−1636.

[32] Signal transduction analysis in ovarian cancer (Stapover) [EB/OL]. Bethesda: National Library of Medicine, 2018 [2018-03-30]. https://www.clinicaltrials.gov/ct2/show/NCT03458221?term=itraconazole&draw=2&rank=138.html.

[33] Rudin CM, Brahmer JR, Juergens RA, et al. Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer [J]. J Thorac Oncol, 2013, 8: 619−623.

[34] Phase 1/2 study of ThermoDox with approved hyperthermia in treatment of breast cancer recurrence at the chest wall (Dignity) [EB/OL]. Bethesda: National Library of Medicine, 2009 [2018-03-30]. https://www.clinicaltrials.gov/ct2/show/NCT00826085?term=ThermoDOX&rank=1.html.

[35] Pang X, Du HL, Zhang HQ, et al. Polymer-drug conjugates: present state of play and future perspectives [J]. Drug Discov Today, 2013, 18: 1316−1322.

[36] Tu Y, Zhu L. Enhancing cancer targeting and anticancer activity by a stimulus-sensitive multifunctional polymer-drug conjugate [J]. J Control Release, 2015, 212: 94−102.

[37] Lu X, Wang QQ, Xu FJ, et al. A cationic prodrug/therapeutic gene nanocomplex for the synergistic treatment of tumors [J]. Biomaterials, 2011, 32: 4849−4856.

[38] Xu J, Du Y, Liu XJ, et al. Recombinant EGFR/MMP-2

bi-targeted fusion protein markedly binding to non-small-cell lung carcinoma and exerting potent therapeutic efficacy [J]. Pharmacol Res, 2017, 126: 66−76.

[39] Yang T, Xu L, Li B, et al. Antitumor activity of a folate receptor-targeted immunoglobulin G-doxorubicin conjugate [J]. Int J Nanomed, 2017, 12: 2505−2515.

[40] Calixto G, Bernegossi J, Fonseca-Santos B, et al. Nanotechnology-based drug delivery systems for treatment of oral cancer: a review [J]. Int J Nanomed, 2014, 9: 3719−3735.

[41] Chiang YT, Lo CL. pH-responsive polymer-liposomes for intracellular drug delivery and tumor extracellular matrix switched-on targeted cancer therapy [J]. Biomaterials, 2014, 35: 5414−5424.

[42] Li Y, Gao GH, Lee DS. Stimulus-sensitive polymeric nanoparticles and their applications as drug and gene carriers [J]. Adv Healthc Mater, 2013, 2: 388−417.

[43] Patil Y, Amitay Y, Ohana P, et al. Targeting of pegylated liposomal mitomycin C prodrug to the folate receptor of cancer cells: intracellular activation and enhanced cytotoxicity [J]. J Control Release, 2016, 225: 87−95.

[44] Liu H, Xie Y, Zhang Y, et al. Development of a hypoxia-triggered and hypoxic radiosensitized liposome as a doxorubicin carrier to promote synergetic chemo-/radio-therapy for glioma [J]. Biomaterials, 2017, 121: 130−143.

[45] Wang H, Su W, Wang S, et al. Smart multifunctional core-shell nanospheres with drug and gene co-loaded for enhancing the therapeutic effect in a rat intracranial tumor model [J]. Nanoscale, 2012, 4: 6501−6508.

[46] Quader S, Liu X, Chen Y, et al. cRGD peptide-installed epirubicin-loaded polymeric micelles for effective targeted therapy against brain tumors [J]. J Control Release, 2017, 258: 56−66.

[47] Eetezadi S, Ekdawi SN, Allen C. The challenges facing block copolymer micelles for cancer therapy: *in vivo* barriers and clinical translation [J]. Adv Drug Deliv Rev, 2015, 91: 7−22.

[48] Yi XL, Zhang B, Zhang N, et al. Advances in polymer-drug conjugated micelles in the delivery of anticancer drugs [J]. Acta Pharm Sin (药学学报), 2016, 51: 710−716.

[49] Charbgoo F, Alibolandi M, Taghdisi SM, et al. MUC1 aptamer-targeted DNA micelles for dual tumor therapy using doxorubicin and KLA peptide [J]. Nanomedicine, 2018, 14: 685−697.

[50] Li Z, Cai Y, Zhao Y, et al. Polymeric mixed micelles loaded mitoxantrone for overcoming multidrug resistance in breast cancer *via* photodynamic therapy [J]. Int J Nanomed, 2017, 12: 6595−6604.

[51] Biswas S, Kumari P, Lakhani PM, et al. Recent advances in polymeric micelles for anti-cancer drug delivery [J]. Eur J Pharm Sci, 2016, 83: 184−202.

[52] Nakayama M, Akimoto J, Okano T. Polymeric micelles with stimuli-triggering systems for advanced cancer drug targeting [J]. J Drug Target, 2014, 22: 584−599.

[53] Han M, Lv Q, Tang XJ, et al. Overcoming drug resistance of MCF-7/ADR cells by altering intracellular distribution of doxorubicin *via* MVP knockdown with a novel siRNA polyamidoamine-hyaluronic acid complex [J]. J Control Release, 2012, 163: 136−144.

[54] Wang M, Li Y, Huang F. Pluronic-attached polyamidoamine dendrimer conjugates overcome drug resistance in breast cancer [J]. Nanomedicine (Lond), 2016, 11: 2917−2934.

[55] Taghdisi SM, Danesh NM, Ramezani M, et al. Double targeting and aptamer-assisted controlled release delivery of epirubicin to cancer cells by aptamers-based dendrimer *in vitro* and *in vivo* [J]. Eur J Pharm Biopharm, 2016, 102: 152−158.

[56] Sahu P, Kashaw SK, Kushwah V, et al. pH responsive biodegradable nanogels for sustained release of bleomycin [J]. Bioorg Med Chem, 2017, 25: 4595−4613.

[57] Wang Y, Luo Y, Zhao Q, et al. An enzyme-responsive nanogel carrier based on PAMAM dendrimers for drug delivery [J]. ACS Appl Mater Interfaces, 2016, 8: 19899−19906.

[58] Danesh NM, Lavaee P, Ramezani M, et al. Targeted and controlled release delivery of daunorubicin to T-cell acute lymphoblastic leukemia by aptamer-modified gold nanoparticles [J]. Int J Pharm, 2015, 489: 311−317.

[59] Hanafi-Bojd MY, Jaafari MR, Ramezanian N, et al. Surface functionalized mesoporous silica nanoparticles as an effective carrier for epirubicin delivery to cancer cells [J]. Eur J Pharm Biopharm, 2015, 89: 248−258.

[60] Yang M, Liu Y, Hou W, et al. Mitomycin C-treated human-induced pluripotent stem cells as a safe delivery system of gold nanorods for targeted photothermal therapy of gastric cancer [J]. Nanoscale, 2017, 9: 334−340.

[61] Liu Y, Yang M, Zhang J, et al. Human induced pluripotent stem cells for tumor targeted delivery of gold nanorods and enhanced photothermal therapy [J]. ACS Nano, 2016, 10: 2375−2385.

[62] Meng H, Mai WX, Zhang H, et al. Codelivery of an optimal drug/siRNA combination using mesoporous silica nanoparticles to overcome drug resistance in breast cancer *in vitro* and *in vivo* [J]. ACS Nano, 2013, 7: 994−1005.

[63] Chapius J, Schmaltz R, Tsosie K. Carbonhydrote dependent targeting of cancer cells by bleomycin-microbubbule conjugates [J]. J Am Chem Soc, 2009, 131: 2438−2429.

[64] Shen YY, Gao ZG, Rapoport N. Recent advances in the applications of ultrasonic microbubbules as gene or drug vectors [J]. Acta Pharm Sin (药学学报), 2009, 44: 961−966.

[65] Luo W, Wen G, Yang L, et al. Dual-targeted and pH-sensitive doxorubicin prodrug-microbubble complex with ultrasound for tumor treatment [J]. Theranostics, 2017, 7: 452−465.

[66] Chang RS, Suh MS, Kim S, et al. Cationic drug-derived nanoparticles for multifunctional delivery of anticancer siRNA [J]. Biomaterials, 2011, 32: 9785−9795.

[67] Taghavi S, Ramezani M, Alibolandi M, et al. Chitosan-modified PLGA nanoparticles tagged with 5TR1 aptamer for *in vivo* tumor-targeted drug delivery [J]. Cancer Lett, 2017, 400: 1−8.

[68] Hadinoto K, Sundaresan A, Cheow WS. Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review [J]. Eur J Pharm Biopharm, 2013, 85: 427−443.

[69] Zhang L, Liu Z, Yang K, et al. Tumor progression of non-small cell lung cancer controlled by albumin and micellar nanoparticles of itraconazole, a multitarget angiogenesis inhibitor [J]. Mol Pharm, 2017, 14: 4705−4713.

[70] Larson N, Roberts S, Ray A, et al. *In vitro* synergistic action of geldanamycin- and docetaxel-containing HPMA copolymer-RGDfK conjugates against ovarian cancer [J]. Macromol Biosci, 2014, 14: 1735−1747.

[71] Tai W, Chen Z, Barve A, et al. A novel rapamycin-polymer conjugate based on a new poly(ethylene glycol) multiblock copolymer [J]. Pharm Res, 2014, 31: 706−719.

[72] Camacho KM, Kumar S, Menegatti S, et al. Synergistic antitumor activity of camptothecin-doxorubicin combinations and their conjugates with hyaluronic acid [J]. J Control Release, 2015, 210: 198−207.

[73] Yoon S, Kim WJ, Yoo HS. Dual-responsive breakdown of nanostructures with high doxorubicin payload for apoptotic anticancer therapy [J]. Small, 2013, 9: 284−293.

[74] Wang R, Li L, Zhang S, et al. A novel enediyne-integrated antibody-drug conjugate shows promising antitumor efficacy against CD30(+) lymphomas [J]. Mol Oncol, 2018, 12: 339−355.

[75] Li W, Li X, Huang T, et al. Engineered production of cancer targeting peptide (CTP)-containing C-1027 in *Streptomyces globisporus* and biological evaluation [J]. Bioorg Med Chem, 2016, 24: 3887−3892.

[76] Yu L, Lu Y, Liu Y. Promiximab-duocarmycin, a new CD56 antibody-drug conjugate, is highly efficacious in small cell lung cancer xenograft models [J]. Oncotarget, 2017, 9: 5197−5207.

[77] Ricart AD. Antibody-drug conjugates of calicheamicin derivative: gemtuzumab ozogamicin and inotuzumab ozogamicin [J]. Clin Cancer Res, 2011, 17: 6417−6427.

[78] Li Q, Li W, Di H, et al. A photosensitive liposome with NIR light triggered doxorubicin release as a combined photodynamic-chemo therapy system [J]. J Control Release, 2018, 277: 114−125.

[79] Zhao Y, Ren W, Zhong T, et al. Tumor-specific pH-responsive peptide-modified pH-sensitive liposomes containing doxorubicin for enhancing glioma targeting and anti-tumor activity [J]. J Control Release, 2016, 222: 56−66.

[80] Lu T, Lokerse WJM, Seynhaeve ALB, et al. Formulation and optimization of idarubicin thermosensitive liposomes provides ultrafast triggered release at mild hyperthermia and improves tumor response [J]. J Control Release, 2015, 220: 425−437.

[81] Nguyen HT, Tran TH, Thapa RK, et al. Targeted co-delivery of polypyrrole and rapamycin by trastuzumab-conjugated liposomes for combined chemo-photothermal therapy [J]. Int J Pharm, 2017, 527: 61−71.

[82] Perillo E, Allard-Vannier E, Falanga A, et al. Quantitative and qualitative effect of gH625 on the nanoliposome-mediated delivery of mitoxantrone anticancer drug to HeLa cells [J]. Int J Pharm, 2015, 488: 59−66.

[83] Hu FQ, Meng P, Dai YQ, et al. PEGylated chitosan-based polymer micelle as an intracellular delivery carrier for anti-tumor targeting therapy [J]. Eur J Pharm Biopharm, 2008, 70: 749−757.

[84] Shi S, Zhu X, Guo Q, et al. Self-assembled mPEG-PCL-*g*-PEI micelles for simultaneous codelivery of chemotherapeutic drugs and DNA: synthesis and characterization *in vitro* [J]. Int J Nanomed, 2012, 7: 1749−1759.

[85] Qiao H, Zhu Z, Fang D, et al. Redox-triggered mitoxantrone prodrug micelles for overcoming multidrug-resistant breast cancer [J]. J Drug Target, 2017, 26: 75−85.

[86] Ma B, Zhuang W, Wang Y, et al. pH-sensitive doxorubicin-conjugated prodrug micelles with charge-conversion for cancer therapy [J]. Acta Biomater, 2018, 70: 186−196.

[87] Saxena V, Hussain MD. Formulation and *in vitro* evaluation of 17-allyamino-17-demethoxygeldanamycin (17-AAG) loaded polymeric mixed micelles for glioblastoma multiforme [J]. Colloids Surf B Biointerf, 2013, 112: 350−355.

[88] Onyuksel H, Mohanty PS, Rubinstein I. VIP-grafted sterically stabilized phospholipid nanomicellar 17-allylamino-17-demethoxy geldanamycin: a novel targeted nanomedicine for breast cancer [J]. Int J Pharm, 2009, 365: 157−161.

[89] Hill EE, Kim JK, Jung Y, et al. Integrin alpha V beta 3 targeted dendrimer-rapamycin conjugate reduces fibroblast-mediated

prostate tumor progression and metastasis [J]. J Cell Biochem, 2018. DOI: 10.1002/jcb.26727.

[90] Kaneshiro TL, Lu ZR. Targeted intracellular codelivery of chemotherapeutics and nucleic acid with a well-defined dendrimer-based nanoglobular carrier [J]. Biomaterials, 2009, 30: 5660−5666.

[91] Huang P, Zhang Y, Wang W, et al. Co-delivery of doxorubicin and (131)I by thermosensitive micellar-hydrogel for enhanced *in situ* synergetic chemoradiotherapy [J]. J Control Release, 2015, 220: 456−464.

[92] Stead SO, McInnes SJP, Kireta S, et al. Manipulating human dendritic cell phenotype and function with targeted porous silicon nanoparticles [J]. Biomaterials, 2018, 155: 92−102.

[93] Rochani AK, Balasubramanian S, Ravindran GA, et al. Dual mode of cancer cell destruction for pancreatic cancer therapy using Hsp90 inhibitor loaded polymeric nano magnetic formulation [J]. Int J Pharm, 2016, 511: 648−658.

[94] Shi F, Li M, Wu S, et al. Enhancing the anti-multiple myeloma efficiency in a cancer stem cell xenograft model by conjugating the ABCG2 antibody with microbubbles for a targeted delivery of ultrasound mediated epirubicin [J]. Biochem Pharmacol, 2017, 132: 18−28.

[95] Evangelatov A, Skrobanska R, Mladenov N, et al. Epirubicin loading in poly(butyl cyanoacrylate) nanoparticles manifests *via* altered intracellular localization and cellular response in cervical carcinoma (HeLa) cells [J]. Drug Deliv, 2016, 23: 2235−2244.

[96] Zhong Y, Zhang J, Cheng R, et al. Reversibly crosslinked hyaluronic acid nanoparticles for active targeting and intelligent delivery of doxorubicin to drug resistant CD44+ human breast tumor xenografts [J]. J Control Release, 2015, 205: 144−154.

[97] Xu Y, Asghar S, Gao S, et al. Polysaccharide-based nanoparticles for co-loading mitoxantrone and verapamil to overcome multidrug resistance in breast tumor [J]. Int J Nanomed, 2017, 12: 7337−7350.

[98] Dhandhukia JP, Li Z, Peddi S, et al. Berunda polypeptides: multi-headed fusion proteins promote subcutaneous administration of rapamycin to breast cancer *in vivo* [J]. Theranostics, 2017, 7: 3856−3872.

[99] Hou Z, Zhan C, Jiang Q, et al. Both FA- and mPEG-conjugated chitosan nanoparticles for targeted cellular uptake and enhanced tumor tissue distribution [J]. Nanoscale Res Lett, 2011, 6: 563.

[100] Nafee N, Hirosue M, Loretz B, et al. Cyclodextrin-based star polymers as a versatile platform for nanochemotherapeutics: enhanced entrapment and uptake of idarubicin [J]. Colloids Surf B Biointerf, 2015, 129: 30−38.

[101] Zhu QL, Zhou Y, Guan M, et al. Low-density lipoprotein-coupled N-succinyl chitosan nanoparticles co-delivering siRNA and doxorubicin for hepatocyte-targeted therapy [J]. Biomaterials, 2014, 35: 5965−5976.

[102] Kang L, Gao ZG, Huang W. Nanocarrier mediated co-delivery of chemotheraputic drugs and gene agents for cancer treatment [J]. Acta Pharm Sin B, 2015, 5: 169−175.