科学通报 2022 年 第 67 卷 第 14 期: 1517 ~ 1531
《中国科学》杂志社 SCIENCE CHINA PRESS
香山科学会议专栏 评 述
第694次学术讨论会·用于硼中子俘获肿瘤治疗的含硼药物

# 用于硼中子俘获治疗的硼携带剂研究现状

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2021-09-27 收稿, 2021-11-26 修回, 2021-11-29 接受, 2021-11-29 网络版发表
中国核工业集团有限公司领创科研项目资助

**摘要** 硼中子俘获治疗(boron neutron capture therapy, BNCT)是一种用于肿瘤治疗的二元靶向疗法. 从1936年BNCT原理首次被提出至今, 该技术经历了近90年的发展, 是目前治疗恶性脑胶质瘤最有效的方法之一. 而BNCT技术治疗肿瘤能否成功的关键因素之一是能否找到对肿瘤有高靶向性和高亲和力的硼携带剂. 本文对用于BNCT的硼携带剂的国内外研究现状进行了分类、总结和综述, 对各类硼携带剂的特性、研发及转化状态进行了对比分析. 第一代硼携带剂因靶向性差已经被停用; 第二代硼携带剂临床应用最为成熟, 但存在载硼量有限、个体摄取差异大等问题; 第三代硼携带剂载硼量和靶向性均有大幅提升但多处于实验研究阶段, 安全性及有效性有待进一步验证. 本文根据各类硼携带剂的研发现状, 分析判断了阻碍含硼药物研发和临床转化面临的瓶颈: 应用范围有限、市场规模小, 技术壁垒多、评价体系不完整, 归类不清晰、审批难度大等, 并针对各瓶颈问题提出了相应的解决措施和建议. 总之, BNCT技术拥有广阔的应用前景, 希望通过多学科交叉与融合, 推进BNCT技术的综合性研究, 启迪硼携带剂研发和转化的新思路, 促进BNCT技术的临床应用.

**关键词** 硼中子俘获治疗, 肿瘤治疗, 硼携带剂, 转化瓶颈

硼中子俘获治疗(boron neutron capture therapy, BNCT)是一种用于肿瘤治疗的二元靶向疗法, 其原理是将对肿瘤有特异性亲和力的$^{10}$B化合物(硼携带剂)注入人体, 经中子束局部照射使聚集在肿瘤组织中的$^{10}$B与热中子发生核反应, 利用生成的$^{7}$Li与α粒子破坏肿瘤组织(图1). 反应释放的$^{7}$Li粒子的射程约为4~5 μm, α粒子的射程约为9~10 μm, 而肿瘤细胞的直径一般小于10 μm, 所以该方法的辐射杀伤范围仅局限于肿瘤细胞内, 对周围正常组织的损害很小, 因而处于治疗中的患者不需要特殊防护[1]. BNCT疗法的特点主要包括: (1) 肿瘤靶向性好, 局部杀伤剂量大; (2) 对肿瘤细胞造成的损伤不可修复, 不需增氧效应, 可同时杀死富氧细胞、乏氧细胞及未增值的$G_0$期细胞; (3) 治疗肿瘤种类多, 随硼携带剂自身的靶向性及所结合载体靶向性的不同, 除恶性脑胶质瘤外, 还可以治疗其他多种肿瘤. 基于以上特点, 该法成为目前治疗恶性脑胶质瘤和黑色素瘤最有效的方法之一[1].

## 1 硼携带剂的一般要求

用于BNCT的硼携带剂应具备以下特点[2]: (1) 肿瘤靶向性强, 靶(肿瘤组织)和非靶(正常组织)中的$^{10}$B浓度比值(T/N)要高, 至少T/N＞3~4:1; (2) 肿瘤摄取量高且滞留时间长, 不论单独使用还是与其他硼携带剂联合使用, 每个肿瘤细胞中要含$10^9$个$^{10}$B原子或20~50 μg $^{10}$B/g肿瘤组织, 且中子照射时能保持此浓度; (3) 血液清除快、体内毒性低. 目前为止, 用于BNCT的硼携带剂可分为三代. 第一代为可溶性硼酸盐, 由于其全身分布, 肿瘤靶向性差, 因而T/N及T/B均很低, 这类化合物

**引用格式:** 李凤林, 罗志福. 用于硼中子俘获治疗的硼携带剂研究现状. 科学通报, 2022, 67: 1517–1531
Li F L, Luo Z F. Boron delivery agents for boron neutron capture therapy (in Chinese). Chin Sci Bull, 2022, 67: 1517–1531, doi: 10.1360/TB-2021-1013

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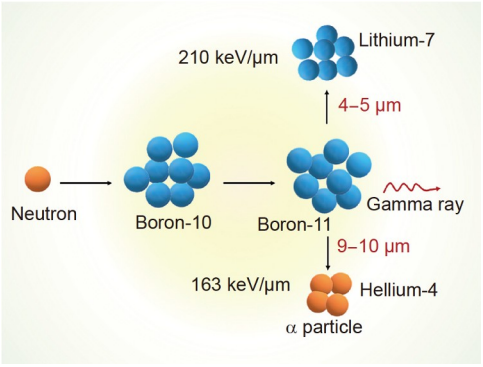


图 1 (网络版彩色)BNCT原理示意图
**Figure 1** (Color online) Schematic presentation of BNCT

于20世纪60年代被停止使用[3~5]. 第二代为有机硼化物, 最具代表性的有巯基十二硼烷二钠盐(sodium borocaptate, BSH)、对二羟基硼酰苯丙氨酸(boronophenylalanine, BPA)以及用于监测体内BPA分布的$^{18}$F-BPA等小分子化合物[6~9]. 另外, 还有多种硼烷及碳硼烷类化合物均表现出较好的肿瘤靶向性. 第三代为各类靶向分子与含硼化合物组成的硼携带剂. 如氨基酸类似物、硼化卟啉、含硼核苷等小分子硼携带剂, 以及含硼化合物与靶向分子螯合而成的脂质体、聚合物等纳米粒子类硼携带剂[10,11].

## 2 第一代硼携带剂

20世纪50年代开始, Soloway[3]合成了大量用于BNCT的小分子含硼化合物, 即第一代硼携带剂. 第一代硼携带剂多为可溶性硼酸盐及其衍生物(图2, **1**~**4**). 1950~1960年, Farr等人[5]利用无机硼携带剂borax或sodium pentaborate开展了恶性胶质细胞瘤, 特别是多形性胶质母细胞瘤(glioblastoma, GBM)的临床治疗. 但这次临床试验最终以失败告终, 患者生存期无明显延长, 失败的主要原因包括中子的穿透性弱、硼携带剂缺乏选择性、肿瘤靶向性差、T/B比值过低. 由于第一代硼携带剂在全身分布, 不在肿瘤中浓集, T/N及T/B均很低, 这类化合物已于20世纪60年代被停止使用[3~5].

## 3 第二代硼携带剂

1958年, Snyder等人[12]首次合成了第二代硼携带剂BPA(图3, **5**), 它最初以病灶旁注射的方式被用于治疗黑色素瘤[13,14]. BPA是酪氨酸类似物, 进入体内后通过酪氨酸羟化酶催化可穿过血脑屏障(blood brain barrier, BBB), 靶向性地在肿瘤细胞中聚集. 但BPA极难溶

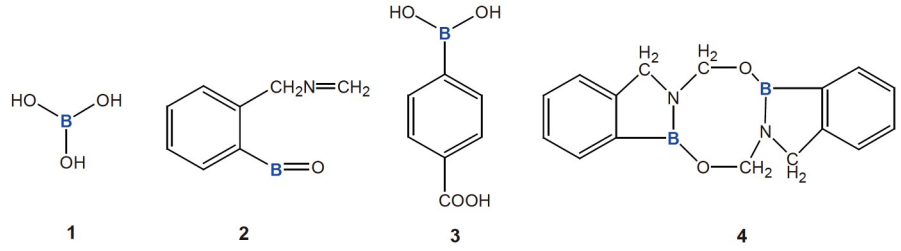


图 2 (网络版彩色)第一代硼携带剂
**Figure 2** (Color online) The first generation of boron delivery agents

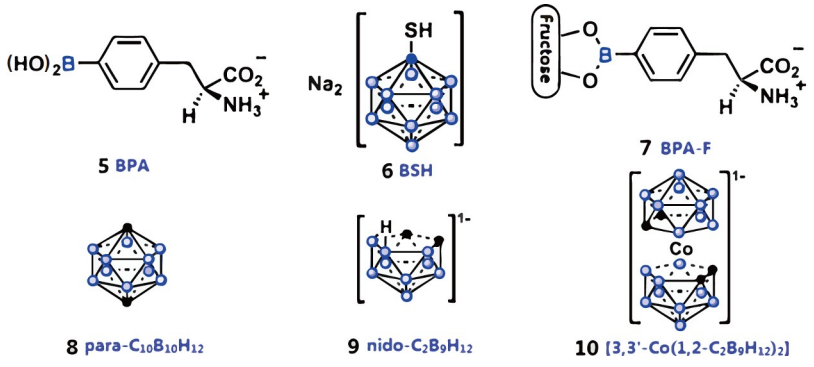


图 3 (网络版彩色)第二代硼携带剂
**Figure 3** (Color online) The second generation of boron delivery agents

于水，只溶于强酸、强碱，为了增加其水溶性，研制了BPA-果糖复合物(BPA-F)(图3，**7**)[15]，随后，以反应堆产生的超热中子为中子源，以BPA-F为硼携带剂，多国开展了治疗高级别神经胶质瘤的BNCT临床试验[16~24]，取得了令人满意的结果. 美国Harvard-MIT BNCT中心在一项临床研究中，用BPA治疗了22例神经胶质母细胞瘤患者，治疗后2例肿瘤完全消除，13例症状明显减轻[20]. 瑞典Studisvk核能研究中心[21]在2001~2003年开展了II期BNCT临床试验，共治疗了52例神经胶质母细胞瘤，取得了较好的治疗效果. 芬兰赫尔辛基大学一项BNCT临床研究，治疗21例恶性脑肿瘤患者，治疗后患者1年生存率超过60%，且副作用远低于常规放疗[22]. 2010年起，新竹“清华大学”和台北荣民总医院开始联合进行头颈部肿瘤的BNCT临床试验[23]，用新竹“清华大学”的反应堆，首次试验治疗10例患者，静脉滴注BPA 400 mg/kg，给药后2 h开始中子照射，治疗后3例患者产生完全应答，4例患者产生部分应答，治疗有效率可达70%. 北京凯百特公司于2014年利用医院中子照射器，静脉滴注BPA 350 mg/kg，进行了黑色素瘤的临床治疗[24]，取得了较好的治疗效果.

目前，BPA是恶性脑胶质瘤、头颈部复发肿瘤及黑色素瘤BNCT治疗的首选药物. 2020年，BPA在日本正式获批用于头颈部肿瘤的BNCT治疗. 但BPA在临床试验中存在个体摄取差异大并导致治疗效果差异也较大的问题. 为了解决这个问题，$^{18}$F-BPA应运而生. $^{18}$F-BPA不仅能研究BPA在体内的代谢过程，更能通过正电子断层扫描(positron emission computed tomography, PET)显像实时掌握BPA在体内的生物分布状态，这对BNCT治疗的时间选择、治疗效果评价有重大意义. 目前$^{18}$F-BPA的PET成像已成为BNCT临床治疗计划的一部分[9].

1967年，Soloway等人[25]首次合成了另一种第二代硼携带剂BSH(图3，**6**). 1968年，Hatanaka[26]最先将BSH用于BNCT临床试验. 之后在日本采用热中子BNCT，他们利用BSH陆续治疗脑胶质瘤患者100余例，其中16例肿瘤体积较小的高级别胶质瘤患者，5年生存率达58%，10年生存率达29%，远超常规放疗的生存率[27,28]. 随后，荷兰、捷克等国家先后开展了BSH治疗高级别神经胶质瘤及黑色素瘤的I/II期临床试验，并尝试将BSH的治疗领域不断扩大至肝癌、肺癌、甲状腺癌、结肠癌以及关节炎等疾病[29,30].

20世纪90年代后，随着合成技术的发展，大量碳硼烷结构(图3，**8~10**)[31,32]被成功合成，并显示出强大的BNCT硼携带剂潜力. 这主要由于其独特的分子性能：含硼量高、既可亲水亦可亲脂性、结构稳定性和光化学稳定性高，以及易于与其他功能性分子偶联而制备不同的肿瘤靶向分子. 同时，该类化合物为第三代靶向硼携带剂的发展奠定了重要基础，在第三代硼携带剂中作为硼供体而被广泛应用.

作为已被临床使用多年的BNCT硼携带剂，BPA和BSH在临床使用中存在的主要问题是，肿瘤摄取存在明显的个体差异[33,34]，尤其是脑肿瘤. 导致BPA和BSH肿瘤摄取差异大的原因主要是高级别神经胶质瘤本身在组织学、基因组学和表观遗传学等方面均存在差异[35]，另外患者的个体吸收差异也有一定影响. 这使得BNCT治疗后患者的平均生存时间(mean survival time, MST)存在很大差异，临床治疗标准难以统一，这也是BPA、BSH临床应用发展缓慢的原因之一. 因此，BPA和BSH在临床应用时，要根据患者的个体差异及肿瘤特点，选择对药物吸收好的病例，因人而异地制定精准治疗方案才可能取得好的治疗效果.

BPA、BSH临床应用70余年，但全球只进行了千余例病例，进展十分缓慢. 阻碍其发展和临床应用的主要问题有：2000年以前，BNCT所需要的中子源主要依靠大型核反应堆产生，无法在医院及医疗中心普及，导致其临床应用范围有限、市场规模小；临床医生和民众对BNCT技术接受度低，使得临床病例筛选困难，同时治疗效果个体差异大、治疗标准难以统一，严重影响了其临床应用的开展；医药企业对BPA、BSH的市场规模和发展前景严重低估，导致BPA、BSH的价格相对较高，进一步影响了其产业化发展. 另外，BNCT技术在治疗过程中涉及中子源、放射性药物、放射性剂量计算及监测、辐射生物学等多种学科的交叉和融合，需要多体系联合运行才能保证治疗效果，但目前各评价体系均不完善，直接限制了BNCT技术的发展.

## 4 第三代硼携带剂

鉴于前两代硼携带剂没能完全满足理想硼携带剂的要求，科研人员需要继续研发新的更理想的硼携带剂. 随着有机合成技术、生物偶联技术以及肿瘤病理组织学的发展，大量第三代硼携带剂被研发出来. 第三代硼携带剂以提高肿瘤靶向性及载硼量为主要目标，多为各类靶向分子与含硼化合物螯合而成的硼携带剂，包括氨基酸类似物、硼化卟啉、含硼核苷等小分子硼

携带剂, 以及含硼化合物与靶向分子螯合而成的脂质体、聚合物等纳米粒子类硼携带剂[10,11]等.

### 4.1 氨基酸及多肽类硼携带剂

#### 4.1.1 氨基酸类硼携带剂

用各种含硼物质(如硼酸、硼烷和硼簇化合物)对天然和非天然氨基酸进行硼化, 即成为氨基酸类硼携带剂. 氨基酸类硼携带剂可被依赖氨基酸生长的肿瘤细胞优先摄取[36]. 如硼化的*L*-酪氨酸(B-*L*-Tyr)和*L*-多巴(B-*L*-DOPA)(图4, **11**, **12**)作为酪氨酸酶与黑色素前体的底物, 与BPA相比, 在酪氨酸酶高表达的细胞系(SK-23mel细胞)中的摄取显著增加, 同时对富含酪氨酸酶的黑色素瘤细胞的选择性也更高[37].

与天然氨基酸相比, 非天然氨基酸具有更高的代谢稳定性. Hattori等人[38,39]设计并合成了一系列含BSH的氨基酸衍生物, 如BSH-α-氨基酸(图4, **13**)、BSH-α,α-环烷氨基酸(图4, **14**, **15**), 它们具有较低的细胞毒性, 可以聚集在细胞核边缘, 是理想的BNCT硼携带剂. 与BPA及其衍生物相比, 该类硼携带剂能向多种*L*型氨基酸转运体(LATs)高表达的细胞系(C6,U81)中转运更多的硼. 同时研究发现, *trans*-ACBC-BSH在胶质瘤细胞中的摄取明显高于*cis*-ACBC-BSH, 表明反式结构与1-氨基环丁烷-1-羧酸(ACBC)更接近, 可通过胶质瘤细胞中的LATs转运[40,41].

如图4所示, Kabalka和Yao[42]与Svantesson等人[43]开发了基于环状氨基酸的硼携带剂(图4, **16**~**19**), 在LATs高表达的高级别胶质瘤中, 该类硼携带剂能够穿过BBB, 增加其肿瘤摄取, 且顺式衍生物显示出更高的肿瘤/血液和肿瘤/脑比值. 同时, 由于这些衍生物水溶性强, 进入肿瘤细胞后不能代谢, 提高了其在肿瘤中的滞留时间. 这些优异的性能使含硼环状氨基酸成为理想的硼携带剂, 尤其适用于高级别胶质瘤. Li等人[44]近两年研发了一系列非天然氨基酸类的硼携带剂, 并对其进行$^{18}$F标记用于PET显像, 取得了较好的效果.

#### 4.1.2 多肽类硼携带剂

含硼多肽能与肿瘤细胞中过度表达的受体或转运体结合, 并具有很高的亲和力与选择性, 因而具有靶向硼携带剂的巨大潜力. 用闭式碳硼烷(图5, **20**)取代原肽(如糜蛋白酶、脑啡肽、缓激肽、血管紧张素II、神经肽Y(NPY)等[45])序列中的苯丙氨酸, 实验证明取代后的多肽对相应受体仍具有较高的亲和力. 而闭式碳硼烷取代苯丙氨酸的可行性取决于受体结合域能否耐受闭式碳硼烷及是否与其疏水性相匹配.

NPY是大脑中最丰富的神经激素之一, 由36个氨基酸组成[46]. NPY与Y受体(有Y1、Y2、Y4、Y5四种亚型)的亲和力很高, 而hY1受体亚型在85%的原发性乳腺肿瘤和100%的淋巴结转移肿瘤中被发现[47]. Ahrens等人[48]开发了含碳硼烷的NPY复合物及其衍生物, 其中衍生物[F$^7$,P$^{34}$]-NPY(图5, **21**)能优先与hY1受体结合, 将其与碳硼烷改性过的*L*-赖氨酸偶联得到的[K$^4$-N]-[F$^7$,P$^{34}$]-NPY(图5, **22**)在细胞中的亲和力达纳摩尔级, 并能选择性内化.

整合素$\alpha_v\beta_3$在大多肿瘤细胞中均有高表达, 而含有Arg-Gly-Asp(RGD)序列的肽能与其特异性结合, 因此RGD是肿瘤诊疗中最具吸引力的多肽之一[49]. c(RGDfV)是第一个具有高选择性和高活性的$\alpha_v\beta_3$拮抗剂, 随后c(RGDfK)和c(RGDfC)相继被研发, 其结构中赖氨酸或半胱氨酸残基均能被功能性氨基或巯基修饰[50,51]. Kimura等人[52]将c(RGDfK)与BSH或1,2-二碳-碳硼烷偶联制备了一系列复合物(图5, **23**~**25**), 与BSH或c(RGDfK)

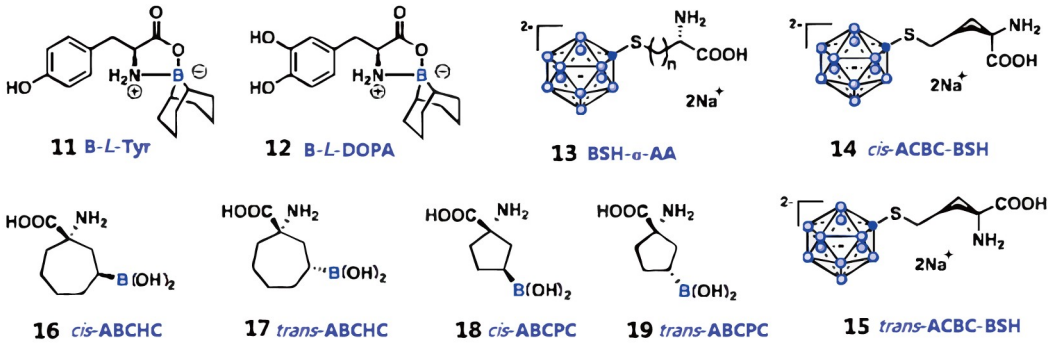


图 4 (网络版彩色)氨基酸类硼携带剂的结构
**Figure 4** (Color online) The structures of boron delivery agents of amino acid

相比，复合物具有更高的肿瘤摄取和更慢的肿瘤清除率.

Iguchi等人[53]将BSH与短精氨酸肽偶联制备BSH-3R，并对其进行$^{64}$Cu标记，得到放射性显像剂$^{64}$Cu-BSH-3R-DOTA(图5, **26**)，通过PET显像可得到BSH-3R在脑肿瘤模型动物体内的生物分布，该复合物在给药后6和24 h, 肿瘤/脑的比值可达15.5.

### 4.2 卟啉衍生物类硼携带剂

卟啉衍生物作为硼携带剂具有以下特点[54]: (1) 卟啉可以与肿瘤DNA结合形成复合物，从而使卟啉类硼携带剂在肿瘤中的摄取和滞留时间大大提高; (2) 多个硼团簇可以附着在一个卟啉骨架上，载硼量高; (3) 可选择性地靶向肿瘤，从而使T/B和T/N比值高; (4) 某些卟啉衍生物具有光学性质，可用于监测硼的分布状态; (5) 含硼卟啉衍生物在肿瘤细胞中可以被BNCT治疗时的低能中子或红光触发而用于光动力治疗(photodynamic therapy, PDT). 由于这些特点, 卟啉类硼携带剂受到越来越多的关注.

Miura研究团队[55~57]自1992年以来，开发了一系列亲脂性、金属络合卟啉类硼携带剂. 其中Cu(II)和Zn(II)与含硼卟啉络合，形成CuTCPH和ZnTCPH(图6,

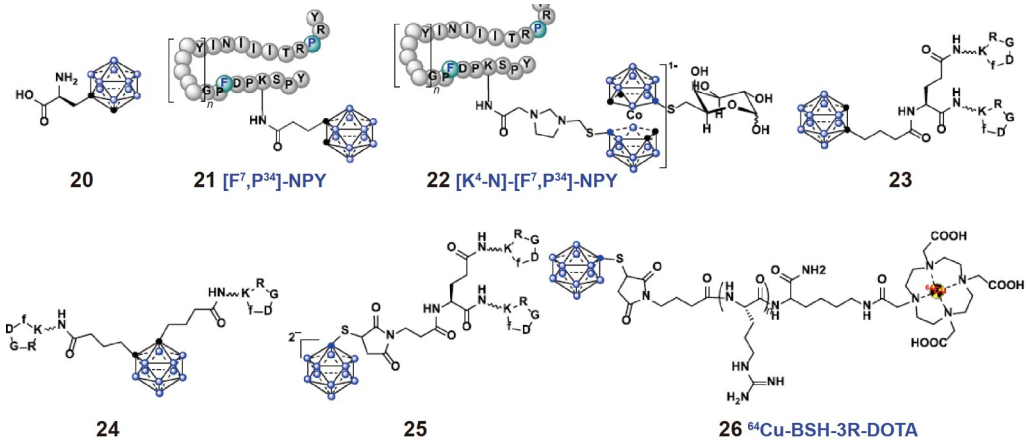


**图 5** (网络版彩色)多肽类硼携带剂的结构
**Figure 5** (Color online) The structures of boron delivery agents of peptides

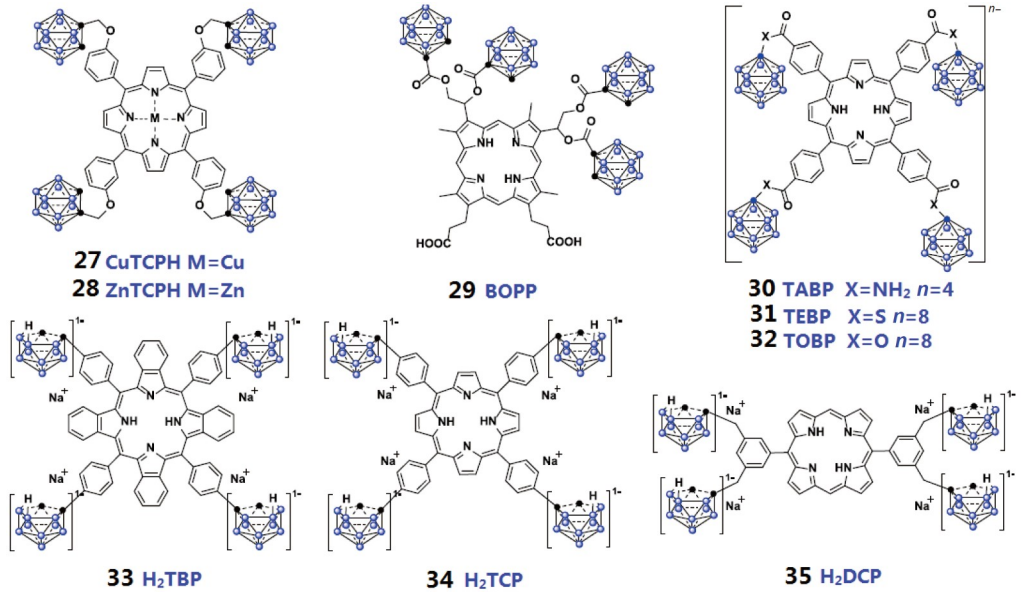


**图 6** (网络版彩色)卟啉类硼携带剂的结构
**Figure 6** (Color online) The structures of boron delivery agents of porphyrin derivatives

**27**, **28**), 是目前研究最充分的卟啉衍生物类硼携带剂. CuTCPH和ZnTCPH在荷EMT-6肿瘤小鼠体内的生物分布类似[55], T/B和T/N比值都比较高(分别为60:1和8:1), 但肝脏摄取也较高. 此外, 注射ZnTCPH后, 荷瘤鼠的脾脏、肝脏和肿瘤均有荧光出现, 可用于光学诊疗. 同时, CuTCPH或ZnTCPBr用$^{67}$Cu或$^{64}$Cu标记后, 可通过单光子发射断层扫描(single photon emission computed tomography, SPECT)或PET用于肿瘤显像诊断.

BOPP(图6, **29**)分子中约30%的重量为硼元素, 水溶性高, 对肿瘤有靶向定位作用. 中国原子能科学研究院曾开展了BOPP的合成及动物评价, 并探索了BOPP的氚标记, 用于体内药物含量的测量. 有学者对BOPP在荷不同肿瘤动物模型中的分布和代谢等进行了研究[58~60]. BOPP作为早期高级别胶质瘤光动力治疗剂已进入I期临床试验, Rosenthal等人[61]对BOPP的给药剂量、体内毒性以及药代动力学特性进行了评估, 为其在BNCT中的应用提供了参考.

Ozawa等人[62]开发了一系列含碳硼烷结构的卟啉类硼携带剂TABP、TEBP和TOBP(图6, **30**~**32**), 并对其在体内的生物学特性及用于BNCT的可行性进行了评价. 有学者评估了水溶性化合物$H_2$TBP、$H_2$TCP和$H_2$DCP(图6, **33**~**35**)在黑色素瘤B16F1细胞中的光敏能力和定位能力[63~65], 并对$H_2$TBP和$H_2$TCP在荷F98胶质瘤大鼠体内的生物分布进行了研究, 评价了其用于BNCT治疗的可行性. 研究发现, 经颅内对流增强给药(convection-enhanced delivery, CED), 给药24 h后肿瘤内硼浓度异常高(达100 μg/g), 但中子照射后, 接受$H_2$TBP和$H_2$TCP组大鼠的MST与注射BPA的却无显著性差异. Kawabata等人[66]进一步对大鼠的脑组织进行组织学检查, 研究显示这些卟啉类硼携带剂主要位于巨噬细胞而非肿瘤细胞中. 因此, 若想提高BNCT治疗效果, 需要设计巨噬细胞亲和力更低且肿瘤摄取更高的卟啉类硼携带剂.

### 4.3 核苷类硼携带剂

核苷类硼携带剂能特异性靶向表达胸苷激酶1 (thymidine kinase-1, TK1)的肿瘤细胞, 并进入肿瘤细胞的DNA. TK1可以催化胸腺嘧啶核苷(Thd)和2-脱氧尿苷(dUrd)的磷酸化, 是细胞分裂和扩散过程中DNA复制的重要酶[67,68]. 硼化Thd和dUrd衍生物是TK1的有利底物, 经TK1磷酸化后可将硼引入肿瘤细胞的DNA, 从而增加BNCT的相对生物学效应(relative biological effectiveness, RBE)[69]. Al-Madhoun等人[70]发现N-3位被碳硼烷结构取代的胸苷衍生物(图7, **36**, **37**)仍可以被TK1磷酸化. 随后, Al-Madhoun等人[71,72]和Byun等人[73]选择N5-2OH(图7, **38**)在荷F98胶质瘤大鼠中进行了生物分布研究, 结果表明, 肿瘤和正常脑组织中硼含量比值可达8.5. 有学者对荷RG2胶质瘤的大鼠分别注射BPA、N5-2OH及两者联用后进行BNCT治疗, 大鼠的MST分别为35.0±3.3、45.6±7.2和52.9±8.9 d[74,75]. 目前有关N5-2OH的临床试验结果并不理想, 这可能与其胞内流出和代谢有关[76]. Semioshkin等人[77]用$[B_{12}H_{12}]^{2-}$硼化dUrd得到了一系列核苷类硼携带剂(图7, **39**~**41**), 该系列衍生物均表现出较低的细胞毒性、较高的肿瘤摄取, 具备用于BNCT治疗的潜力.

### 4.4 纳米粒子类硼携带剂

纳米粒子因其独特的物理化学和光学特性、能与多种肿瘤靶向配体结合以及可扩展的多功能性等, 成为新型硼携带剂的研究热点[78~80]. 目前纳米粒子类的硼携带种类繁多, 比较有优势的有树状大分子类、脂质体类、聚合物类硼携带剂. 它们的优点是含硼量高, 体内半衰期长、肿瘤蓄积高, 溶解度和药代动力学可根据需要改善, 连接不同靶向分子可靶向不同肿瘤; 缺点是直径过大时无法穿过BBB, 脑肿瘤的摄取有限, 直径大于100 nm时会被巨噬细胞清除, 从而降低肿瘤摄取.

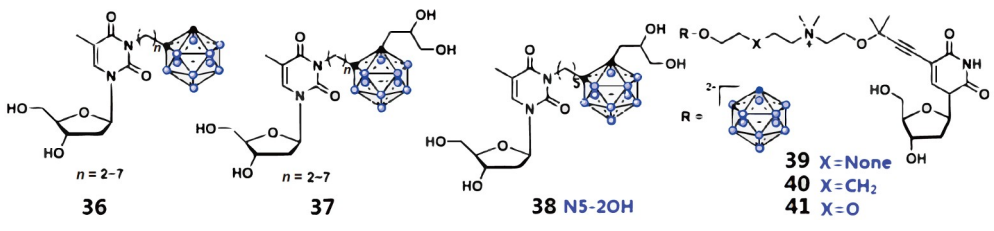


图 7 (网络版彩色)核苷类硼携带剂的结构
**Figure 7** (Color online) The structures of boron delivery agents of nucleosides

4.4.1 树状大分子类纳米粒子硼携带剂

聚酰胺-胺型树状大分子(PAMAM)具有毒性低、反应末端基团多样性, 以及主动靶向性等特点, 使得树状大分子成为药物递送及显像应用的理想载体[81,82]. 树状大分子与不同肿瘤靶向分子偶联, 如表皮生长因子(epidermal growth factor, EGF)、叶酸(folic acid, FA)、血管内皮生长因子(vascular endothelial growth factor, VEGF)等[83~86], 能有效改善硼的靶向转运.

研究发现在高级别胶质瘤表面, 表皮生长因子受体(epidermal growth factor receptor, EGFR)会过度表达, 因此Capala等人[83]利用硼化PAMAM(BSD)的巯基与EGF衍生物的马来酰亚胺基团反应, 产生一种稳定的复合物, 该复合物一个分子中含有960个硼原子(图8, **42**). 将该复合物注射给荷$F98_{EGFR}$和$F98_{WT}$的大鼠, 给药后24 h, 肿瘤中的硼浓度分别达到21.1和9.2 μg/g. Yang等人[84]将硼化PAMAM分别与西妥昔单抗和L8A4单抗相连(图8, **43**, **44**), 通过CED方式对荷瘤大鼠给药, 同时静脉注射BPA, 结果发现BNCT治疗组比放射治疗组的MST增加了2~3倍. Backer等人[85]将VEGF与硼化PAMAM螯合, 并用近红外Cy5染料进行标记, 用于体内外的成像研究. 该复合物无细胞毒性, 并与VEGF一样对血管内皮生长因子受体2(VEGFR-2)有高亲和性和反应活性(VEGFR-2在肿瘤新生血管中有高表达).

此外, Shukla等人[86]研究发现, 叶酸修饰的硼化聚乙二醇(PEG)-PAMAM可以降低网状内皮系统(reticuloendothelial system, RES)与单核吞噬细胞系统(mononeuclear phagocyte system, MPS)对该化合物的摄取, 从而使肿瘤部位达到BNCT所需的硼浓度. Parrott等人[87]合成了硼化PAMAM聚酯, 其内部可填充多达16个碳硼烷分子(图8, **45**), 大大提高了向肿瘤输送硼的效率. 这些树状大分子用途广泛, 含硼量可调控, 同时具有优良的溶解性和定位功能, 是极具潜力的硼携带剂.

4.4.2 脂质体类纳米粒子硼携带剂

脂质体是由胆固醇和天然磷脂组成的无毒、通用、球型的纳米粒子载体[88]. 脂质体可以通过增强渗透滞留效应在大多数肿瘤中被动积聚, 从而输送大量含硼化合物至肿瘤组织, 因此作为潜在的硼携带剂被广泛研究[89~91]. Shelly等人[92]研究表明$B_{20}H_{18}^{2-}$可被包裹在脂质体中制备成可溶性钠盐, 由于脂质体阻止了硼烷离子在血液中的释放, 从而可保持较高的T/B比值及较长时间的肿瘤滞留. Feng等人[93]利用蛋白A(ZZ)抗体亲和支架将含镍脂质体与抗EGFR抗体连接, 再与BSH螯合制备成了免疫脂质体(图9(a)), 可有效地将BSH转运至EGFR过表达的胶质瘤细胞中. Pan等人[94]使用胆固醇介导的胶束(马来酰亚胺-聚乙二醇-胆固醇, mal-PEG-chol)将西妥昔单抗掺入脂质体中, 开发了靶向EGFR的西妥昔单抗脂质体(图9(b)), 该靶向脂质体在胶质瘤细胞中的摄取是非靶向免疫脂质体的8倍.

Kueffer等人[95]将亲脂性碳硼烷化合物K[*nido*-7-$CH_3(CH_2)_{15}$-7,8-$C_2B_9H_{11}$](MAC)嵌入脂质体双层外膜, 用亲水性多面体硼烷阴离子$Na_3$[1-(2′-$B_{10}H_9$)-2-$NH_3B_{10}H_8$](TAC)构成水溶性内核, 制备了一种新型的含硼脂质体(图9(c)). 该脂质体在荷乳腺癌肿瘤EMT6小鼠中的生物分布实验显示, 给药后54 h, 肿瘤中硼浓度达67.8 μg/g. Maitz等人[96]将这种含硼脂质体用于荷结肠癌CT26细胞小鼠的BNCT治疗, 结果显示结肠癌肿瘤治疗效果比之前EMT6肿瘤更明显, 并显示出剂量依赖性. 事实上, 利用其他肿瘤靶向配体, 如EGF、转铁蛋

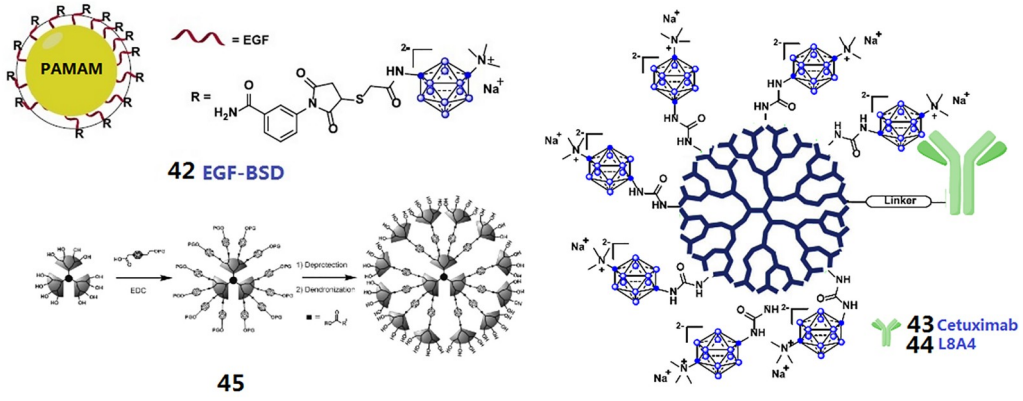


**图 8** 树状大分子类纳米粒子硼携带剂的结构[83~87]
**Figure 8** The structures of boron delivery agents of nanoparticles of PAMAM[83~87]

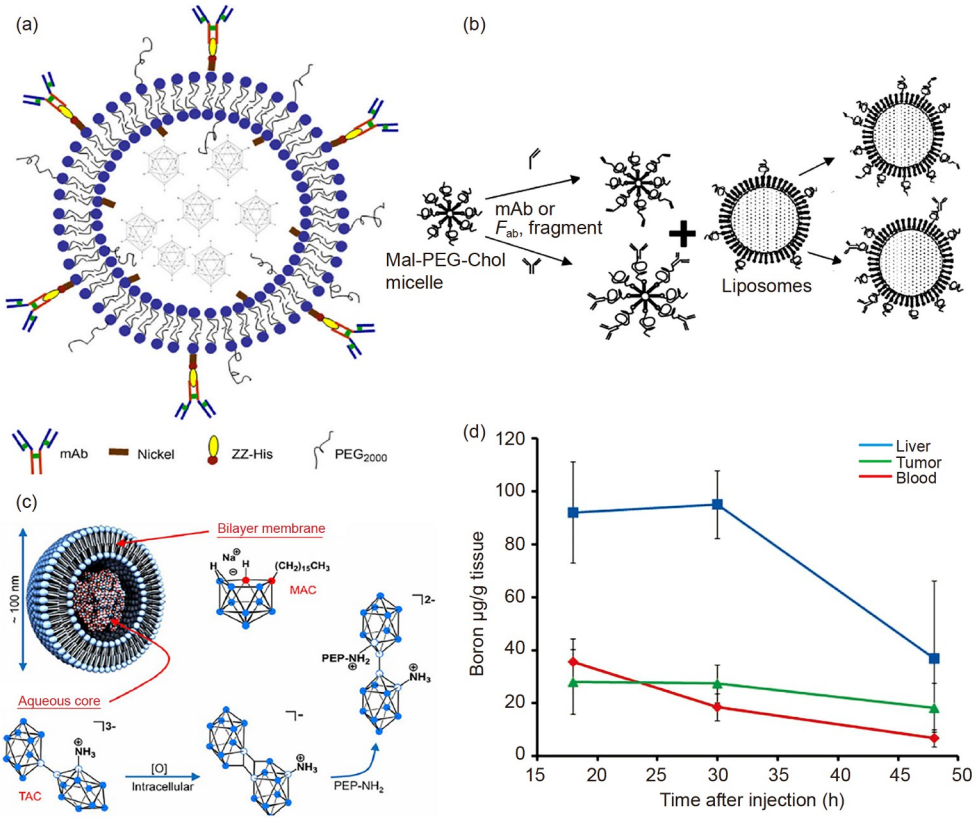


**图 9** 脂质体类纳米粒子硼携带剂的结构[93~95]
**Figure 9** The structures of boron delivery agents of nanoparticles of liposomes[93–95]

白、叶酸等, 可制备许多用于BNCT的靶向脂质体类硼携带剂[97~101].

### 4.4.3 聚合物类纳米粒子硼携带剂

聚合物纳米粒子制备简单、稳定性高、硼化物与其连接可改善其体内溶解度和药代动力学特性, 从而增加体内循环半衰期和肿瘤蓄积, 作为药物载体被广泛研究[102]. Ignatius和Claes[103]研发了聚丙交酯-乙交酯(PLGA), 该聚合物具有优良的生物相容性和降解性, 是极具潜力的药物载体, 特别是对皮肤癌和肺癌. Shi等人[104]将硼化卟啉与PLGA和PEG螯合形成纳米粒子复合物BPN(图10(a)), 并用$^{64}$Cu标记用于PET显像, 使得BPN不仅可以作为硼携带剂用于BNCT治疗, 还可以通过PET显像准确定位恶性肿瘤、评估肿瘤中的硼分布, 实现诊疗一体化.

虽然BSH亲水性高, 但分子量低且带负电, 导致其在肿瘤中的摄取和滞留时间均较低. 为解决此问题, Dewi等人[105]将多聚谷氨酸(P(Glu))、PEG与BSH偶联, 制备了聚合物PEG-b-P(Glu-SS-BSH). 该复合物显著改善了BSH在肿瘤细胞中的摄取, 给药后24 h, 肿瘤中硼浓度比BSH增加了5倍. Mi等人[106]给荷结肠癌C26细胞的小鼠以50 mg/kg静脉注射PEG-b-P, 给药后肿瘤中硼浓度最大可达到90 μg/g, T/B比可达20.

另外, 在BNCT治疗过程中产生的γ射线会使体内产生大量的活性氧(reactive oxygen species, ROS)而导致炎症[107]. 因此, 要尽量减少BNCT过程中ROS的产生以降低其引起的不良反应. Gao等人[108]合成了具有氧化还原功能的纳米粒子硼簇化合物BNP(图10(b)). BNP依靠BSH、带正电的聚合物以及氧化还原反应基团间的静态相互作用而成, 能显著清除ROS, 延长血液循环时间, 增加硼在肿瘤中的积聚及滞留, BNCT治疗后能更有效地抑制肿瘤生长.

### 4.4.4 其他类型纳米粒子硼携带剂

近年来, 除上述几类纳米粒子类硼携带剂, 还有许多其他纳米粒子, 如磁共振成像引导纳米粒子[109]以及由氮化硼组成的无机纳米材料碳纳米管[110,111]、金纳米粒子[112]、磁性纳米粒子[113,114]、类介孔二氧化硅纳

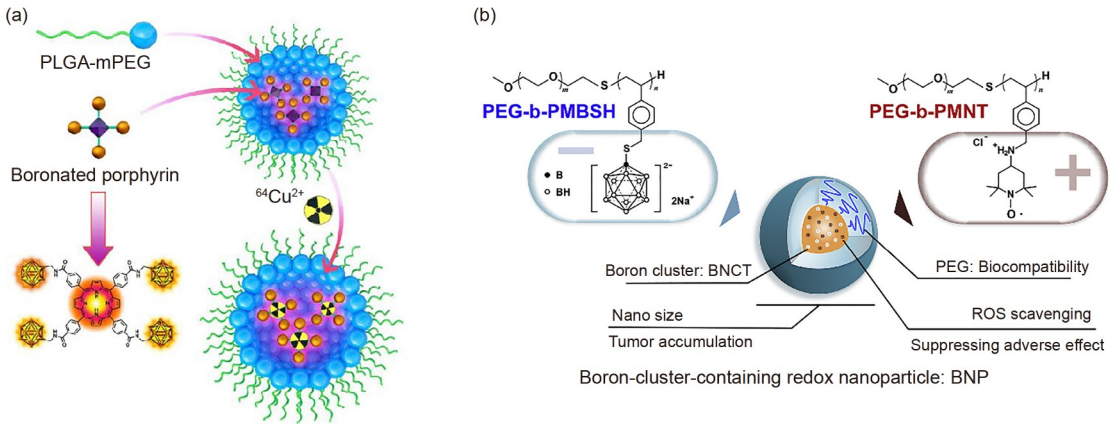


**图 10** 聚合物类纳米粒子硼携带剂的结构[104,108]. (a) 硼化卟啉纳米粒子复合物; (b) 具有氧化还原功能的纳米粒子硼簇化合物
**Figure 10** The structures of boron delivery agents of nanoparticles of polymer[104,108]. (a) Boronated porphyrin nanocomplex; (b) boron cluster-containing redox nanoparticle

米粒子[115]、功能化磷酸硼($BPO_4$)纳米粒子[116]等被应用于BNCT, 均显示出较好的肿瘤摄取及T/N比值, 是极具潜力的BNCT硼携带剂.

总之, 第三代携带剂种类繁多且各具特点: 非天然氨基酸及多肽类硼携带剂代谢稳定性高、在肿瘤中滞留时间更长、靶向性更好、且毒性低、易于合成; 多肽类与硼簇化合物偶联能提高载硼量, 且无免疫原性. 核苷类硼携带剂靶向TK1, 可进入肿瘤细胞的DNA, 因此中子照射后, 射线直接破坏肿瘤细胞的DNA, 放射生物效应更高; 硼化卟啉含硼量高, 水溶性强, 能有效增加肿瘤硼浓度, 而且血药浓度能长时间地保持, 是一种极具优势的携带剂. 基于纳米技术的硼输送系统是高效的硼转运载体, 可通过阻止网状内皮细胞的截获而延长硼携带剂在体内的循环半衰期, 增加硼化物在肿瘤中的摄取, 可有效提高BNCT治疗效果; 且纳米粒子类的硼化物种类繁多, 药代动力学性质可根据需要改善, 连接不同靶向分子可靶向不同肿瘤, 是最具应用前景的硼携带剂.

第三代硼携带剂虽然载硼量大、靶向性好, 但大多仅处于细胞及动物实验等临床前阶段, 其安全性及有效性等需要进一步研究. 但是, 由于硼携带剂具有普通药物和放射性双重特性——硼携带剂本身不具有药效, 进入人体后经过中子照射才开始发挥药效且具有放射性. 而目前关于硼携带的归属尚不清晰, 是按照普通化药或生物药还是按照放射性药物进行监管审批还存在争议, 使得新型含硼药物研究所依据的法规和指导原则不明确, 严重限制了新型含硼药物安全性及有效性评价的进行, 增加了新药审批的难度. 因此第三代硼携带剂的研发和应用亟须尽快明确其归属及相应的指导原则和法规, 以促进其临床转化效率.

## 5 结论与展望

从1936年BNCT原理被提出至今, 已经历了近90年的发展, BPA、BSH临床应用70余年, 但全球只进行了千余例病例, 发展缓慢. 我们分析阻碍BNCT技术及药物研发和应用面临的瓶颈问题主要有以下几点.

(1) BNCT技术应用范围有限、市场规模小. 2000年以前, BNCT所需要的中子源主要依靠核反应堆产生, 据不完全统计, 全球应用于BNCT临床研究的反应堆仅有20座, 其中12座分布在日本和美国, 因此根本无法做到医疗普及, 这是导致BNCT技术临床应用受限的最主要原因. 另外, 临床医生和民众对BNCT技术接受度低, 由于早期中子源均使用大型或较大型研究堆, 不可能建在人口稠密的医疗中心, 加之病患对反应堆的惧怕和排斥, 使得临床病例筛选困难, 严重影响其临床应用的开展. 医药企业对BNCT药物的市场规模和发展前景严重低估, 不愿投资进行含硼药物的研发和产业化, 导致含硼药物的价格相对较高, 进一步限制了BNCT药物的市场推广和产业化进程.

(2) BNCT技术壁垒多, 评价体系不完整. BNCT技术具有二元靶向性, 在治疗过程中同时涉及反应堆或加速器、放射性药物、放射性剂量计算及监测、辐射生物学等多种学科的交叉和融合, 因此技术壁垒多. 其评价体系至少包含中子照射剂量计算系统、体内药物分布及安全性评价体系、体内辐射剂量分布计算系统、治疗计划及效果评估体系等安全性和有效性评价

体系, 但目前各评价体系均不完善, 因此直接影响BNCT技术的临床应用和推广, 是亟须解决的瓶颈问题.

(3) BNCT药物归类不清晰、审批难度大. BNCT药物具有普通药物和放射性双重特性, 含硼药物本身不具有药效, 进入人体经过中子照射后才开始发挥药效且具有放射性. 因此, 其应归属于普通化学药物或生物药物, 还是属于放射性药物的范畴, 目前仍有争议. 这使得成熟的含硼药物(BPA、BSH)在申报时依据的法规和指导原则等不明确, 加大了审批难度. 而新型硼携带剂在研发时就面临无指导原则可参考、遇到技术问题无处可咨询的局面, 进一步增加了新药研发难度、延长了研发周期, 使得新型硼携带剂的产业转化陷入僵局.

未来, BNCT的成功取决于多学科、多技术、多领域的融合与合作对目前瓶颈问题的解决和突破情况. 要想取得成功, 首先要加快新型中子源装置的开发, 加强BNCT技术的推广和科普、提高医生与民众接受度, 扩大BNCT技术适应证的范围. 其次, 要多学科联合研究, 攻克技术壁垒, 建立各评价体系的规范、指南或标准, 形成完善的BNCT治疗系统的安全性和有效性评价体系. 最后, 要加大产学研用的合作, 加强与政府相关部门的沟通, 明确BNCT药物的归属, 制定相应的法规或指导原则, 加快成熟药物BPA、BSH或$^{18}$F-BPA的临床审批及多中心临床试验, 积累临床应用数据以加快其产业化步伐, 同时促进新型含硼药物的研发, 进一步扩展BNCT技术的应用领域.

尽管BNCT技术目前存在一些障碍, 未来也仍存在许多不确定因素, 但毫无疑问, 对头颈部肿瘤及其他传统疗法无效的肿瘤, BNCT仍然是一种理想的治疗方法. 随着日本加速器BNCT治疗系统的正式获批上市, 国内加速器BNCT系统的逐步落地, 以及放射性治疗药物潜在的巨大市场规模, 我们相信BNCT技术拥有广阔的应用前景, 通过学科交叉与融合, 定能推进BNCT技术的整体综合性研究, 启迪BNCT药物研发和转化新思路, 促进BNCT技术的临床应用, 造福患者.

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Summary for “用于硼中子俘获治疗的硼携带剂研究现状”

# Boron delivery agents for boron neutron capture therapy

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Boron neutron capture therapy (BNCT) is a binary method of radiotherapy, which is based on the nuclear reaction that occurs when boron-10 is irradiated with thermal neutron to yield high linear energy transfer α particles and recoiling lithium-7 nuclei. These particles with high energy and short range can kill cancer cells which absorbed $^{10}B$ while little damage to normal tissues. BNCT has experienced nearly 90 years of development since it was first proposed in 1936, which is one of the most effective methods for the treatment of malignant glioma. One of the key factors for the success of BNCT is to find boron delivery agents with high targeting and high affinity to tumors. Currently, although there are various of boron delivery agents, the best compound recognized for BNCT is still boronophenylalanine (BPA), for it has little side effect and no chemistry toxicity. BPA can penetrate the BBB and cell membrane, so it owns higher relative biological effectiveness. BPA is the most widely used BNCT drug in the world, which was officially approved in Japan last year, and the therapeutic effect on glioma is without question. In the past few decades, in order to improve the efficacy of BNCT, significant effort has been devoted to developing new boron delivery agents that possess better uptake and favorable pharmacokinetic characteristics for clinical use.

This review focuses on differents kinds of boron delivery agents developed over the past years, which can be divided into three generations. At present, the first generation of boron delivery agents has been banned for lacking of targeting. The second generation of boron delivery agents is the most mature of the clinical application, but there are some problems need to be solved, such as limited boron loading and individual uptake varies greatly. The third generation of boron delivery agents contains various agents—The boron-containing amino acids and peptides, the boron-containing compound conjugated with nucleosides, porphyrin derivatives, and different types of nanomaterials, was introduced in detail in this review. The boron loading and targeting of the third generation of boron delivery agents have greatly increased, but most of them are still in the experimental stage, and the safety and effectiveness need to be further verified. The advantages and disadvantages of the three generation boron delivery agents were analyzed and compared. Meanwhile, the limitations of the various boron delivery agents were discussed and summarized. Additionally, the prospect and bottleneck of clinical application of these boron delivery agents was critically analyzed from different view of research institutions, pharmaceutical enterprises and government policy. And the corresponding solutions were proposed: (1) Expand the application scope of BPA and BSH; develop new drugs and expand the application fields of BNCT technology; (2) enhance the cooperation of enterprises, universities and research institutions, and promote the clinical approval and application of BPA and BSH; (3) multi disciplines jointly overcome technical barriers and establish a perfect evaluation system of safety and effectiveness for BNCT.

In summary, with the official approval of the Japanese accelerator BNCT treatment system, the application prospects of BNCT technology will be broad all over the world. The comprehensive research of BNCT technology will be promoted by enhancing the intercrossing and coalescence between subjects relative with BNCT, and new ideas will be inspired, all of which will promote the clinical application of BNCT technology, and benefit patients.

**boron neutron capture therapy, oncotherapy, boron delivery agents, bottleneck of translation**

doi: 10.1360/TB-2021-1013