模型引导的药物开发在抗体偶联药物领域的应用

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摘要: 抗体偶联药物 (antibody drug conjugates, ADC) 作为抗肿瘤治疗的前沿技术, 近年来取得了显著进展。ADC通过连接子将高活性小分子毒素与高特异性抗体进行偶联, 不仅能够实现对肿瘤细胞的精准打击, 同时降低了药物的全身毒性, 进而扩大了治疗的有效性和安全性窗口。然而, 由于ADC分子设计的复杂性, 其疗效和安全性受多种因素影响。模型引导的药物开发 (model informed drug development, MIDD) 是一种通过数学和统计模型进行建模和模拟, 对药物研发进行定量分析和决策指导的方法。这种方法为新药研发提供强大的工具支持。通过MIDD整合ADC相关的多方面数据和信息, 有助于理解ADC的复杂机制、药代动力学和药效学等作用特征, 为优化ADC研发流程和临床转化决策提供独特见解。本文将介绍MIDD和ADC的基本概念, 并浅析MIDD在ADC研发不同阶段的应用案例, 旨在为ADC的发展提供有益参考。

关键词: 模型引导的药物开发; 抗体偶联药物; 建模与模拟; 药代动力学/药效动力学; 定量系统药理学; 生理药代动力学; 群体药代动力学

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Application of model informed drug development in the field of antibody drug conjugates

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Abstract: Antibody drug conjugates (ADC) have emerged as a cutting-edge technology in anti-tumor treatment, making significant strides in recent years. ADC couple a highly active small molecule toxin payload to highly specific antibodies through a linker, enabling precise targeting of tumor cells while reducing systemic toxicity, thereby expanding the therapeutic window. However, due to the complexity of ADC molecule design, its efficacy and safety are influenced by various factors. Model-informed drug development (MIDD) is a powerful tool that utilizes various mathematical models for modeling and simulation to conduct quantitative analysis, guiding drug development and decision-making. By integrating multi-faceted data and information using mathematical models, it is possible to gain insights into the complex mechanisms, pharmacokinetics, and pharmacodynamics of ADC, providing unique perspectives for optimizing ADC development processes and clinical translation decisions. This review will introduce the basic concepts of MIDD and ADC and discuss application cases of MIDD in different stages of ADC development, aiming to provide beneficial references for the advancement of ADC.

Key words: model informed drug development; antibody drug conjugate; modeling and simulation; pharmacokinetics/pharmacodynamics; quantitative systems pharmacology; physiologically based pharmacokinetics; population pharmacokinetics

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抗体偶联药物 (antibody drug conjugates, ADC) 是一种新型抗肿瘤药物, 与传统化疗药物相比, 其结合了单克隆抗体的高靶向性和细胞毒素的高活性, 在实现精准高效杀伤肿瘤细胞的同时降低对正常组织的毒副作用。ADC 药物在某些难治性肿瘤中的治疗效果显著优于传统单克隆抗体, 被誉为肿瘤治疗领域的“魔法子弹”[1]。目前, 全球已有 15 款 ADC 成功获批上市 (表 1), 上百种 ADC 正在积极进行临床评估, 充分展现出 ADC 在肿瘤治疗领域的巨大潜力[2]。

ADC 研发管线正在不断被扩大, 大量资源和时间被投入到分子筛选及优化、评估疗效与安全性、实现临床转化以及临床方案设计等关键环节中。鉴于 ADC 药物独特的结构和复杂的作用机制, 仅依赖传统实验方法可能难以甚至无法全面理解各个组成部分对药物疗效及安全性的影响。模型引导的药物研发 (model informed drug development, MIDD) 通过建模与模拟 (modeling and simulation, M&S) 技术整合生理学、药理学和疾病过程等信息通过数学框架进行定量研究, 进而指导新药研发和决策[3-5]。随着 MIDD 在新药研发领域的不断发展, 研究人员意识到将其应用于 ADC 研发将有助于实现这一目标[6,7]。MIDD 为整合 ADC 不同研究阶段、不同维度的数据信息提供了一个定量框架, 进而为药物研发过程中“继续/停止”决策提供了重要的参考依据。这不仅有助于改善现有数据不足的困境, 还能有效提高研发效率, 降低药物研发失败的风险[8,9]。本文将简要介绍 MIDD 和 ADC 的基本概念, 并分析 MIDD 在 ADC 研发不同阶段的应用案例, 旨在为 ADC 的发展提供有益的参考与启示。

1 MIDD 在 ADC 的应用背景

1.1 MIDD 的概念及发展历程 MIDD 是通过 M&S 技术整合生理学、药理学及疾病过程等信息, 进而指导新药研发和决策的定量研究方法。近年来, 随着对

Table 1 List of approved of antibody drug conjugates (ADC). HER2: Human epidermal growth factor receptor 2; Trop-2: Tumor associated antigen 2; BCMA: B-cell maturation antigen; EGFR: Epidermal growth factor receptor; MMAE: Monomethyl muristatin E; PE38: Pseudomonas exotoxin; Dxd: Deruxtecan; PBD: Pyrrolobenzodiazepine; DM: Dexamethasone methylation

Drug name	Trade name	First approved	Indication	Target antigen	Payload	Linker
Gemtuzumab ozogamicin	Mylotarg	2000	CD33-positive acute myeloid leukemia	CD33	Calicheamicins	Cleavable linker acid-labile hydrazone
Brentuximab vedotin	Adcetris	2001	CD30-positive Hodgkin lymphoma and relapsed systemic anaplastic large cell lymphoma	CD30	MMAE	Cleavable linker maleimidocapmyl valine citrulline
Trastuzumab emtansine	Kadcyla	2013	HER2-positive metastatic breast cancer	HER2	DM1	Non-cleavable linker based thioether
Inotuzumab ozogamicin	Besponsa	2017	Relapsed or refractory B-cell acute lymphoblastic leukemia	CD22	Calicheamicins	Cleavable linker acid-labile hydrazone
Moxetumomab pasudotox	Lumoxiti	2018	Relapsed or refractory hairy cell leukemia	CD22	PE38	Cleavable linker mc-vc-PABC
Polatuzumab vedotin	Polivy	2019	Relapsed or refractory diffuse large B-cell lymphoma	CD79B	MMAE	Cleavable linker maleimidocapmyl valine citrulline
Enfortumab vedotin	Padcev	2019	Locally advanced or metastatic urothelial cancer	Nectin-4	MMAE	Cleavable linker maleimidocapmyl valine citrulline
Trastuzumab deruxtecan	Enhertu	2019	Unresectable or metastatic HER2-positive breast cancer	HER2	Dxd	Cleavable linker based tetrapeptide
Sacituzumab govitecan	Trodelvy	2020	Triple-negative breast cancer with relapsed or refractory metastatic disease	Trop-2	SN38	Cleavable carbonate linker
Belantamab mafodotin	Blenrep	2020	Relapsed or refractory multiple myeloma	BCMA	MMAF	Non-cleavable linker maleimidocapryl
Cetuximab sarotalocansodium	Akalux	2020	Unresectable locally advanced or recurrent head and neck cancer	EGFR	IRDye700DX	Non-cleavable linker
Loncastuximab tesirine	Zynlonta	2021	Relapsed or refractory large B-cell lymphoma	CD19	PBD	Cleavable linker valine-alanine
Disitamab vedotin	Aidixi	2021	The integration of a stomach/stomach esophagus adenocarcinoma, breast cancer, urothelial carcinoma	HER2	MMAE	Cleavable linker MC-Val-Cit-PAB
Tisotumab vedotin	Tivdak	2021	Recurrent or metastatic cervical cancer	Tissue factor	MMAE	Cleavable linker valine-citrulline
Mirvetuximab soravtansine	Elahere	2022	FRα-positive platinum-resistant ovarian cancer	FRα	DM4	Cleavable disulfide bond linker

MIDD的认知和价值的不断深化, MIDD已广泛应用于药物研发的各个阶段, 涵盖药物发现、临床前研究、临床开发、监管评估以及药物全生命周期管理, 对药物研发决策的证据支持和指导具有重要意义。模型分析与实测研究过程通常呈现出“学习与确认”循环形式, 即通过已有数据信息建立模型, 预测相关研究结果, 进一步通过后续实测数据验证模型分析结果的可靠性及判断后续研究方向, 并随着研发过程的推进对模型进行不断更新和完善 (图1)[10-13]。

MIDD应用多方面模型工具, 包括群体药代动力学 (population pharmacokinetics, Pop-PK)、生理药动学 (physiologically based pharmacokinetics, PBPK)、药动学/药效学 (pharmacokinetics/pharmacodynamics, PK/PD)、暴露−反应关系 (exposure-response, E-R)、基于模型的荟萃分析 (model-based meta-analysis, MBMA) 及定量系统药理学 (quantitative systems pharmacology, QSP) 等已经在药物研发的多个环节取得了显著的成功应用, 例如适应症与剂量选择、非临床与临床转化研究以及临床药理学研究等方面[14]。

目前, 这些工具在美国FDA批准的药物中的使用比例高达90%以上, 已经成为药物研发领域不可或缺的关键工具。全球众多监管机构包括美国食品药品监督管理局 (Food and Drug Administration, FDA)、国家药品监督管理局药品审评中心 (Center for Drug Evaluation, CDE)、欧洲药品管理局 (European Medicines Agency, EMA)等均发布了多项涉及MIDD的指南和药品申报要求, 这些指导原则旨在鼓励并指导制药企业运用MIDD, 以进一步提升药物的商业、科学和临床价值[15-20]。2018年, FDA在处方药使用者方案第6次修订版 (PDUFA VI)正式认定MIDD为高效和有效药物开发的重要推动因素, 鼓励药物开发人员和美国FDA审查人员能够共同参与讨论药物开发中使用MIDD工具, 有助于药品不同开发环节的研发人员和审评人员就剂量选择、临床试验模拟、机制化安全性评估等方面的决策更早达成共识[15]。CDE于2020年发布的《模型引导的药物研发技术指导原则》将有助于提升国内制药工业界的实践能力, 促进制药行业的技术进步和创新[17]。为了进一步指导我国创新药物临床研究阶段剂量探索和优化, 并提供可参考的技术标准, CDE于2024年7月25日起草了《模型引导的创新药物剂量探索和优化技术指导原则 (征求意见稿)》[20]。

1.2 ADC的结构、作用机制及特征 相较于传统药物, ADC具有独特的结构设计和复杂的作用机制。ADC通常由靶向特异性抗原的单克隆抗体、化学连接子及有效载荷 (小分子毒素) 三部分组成, 每个抗体分子上平均偶联的小分子毒素数量称为抗体药物比 (drug antibody ratio, DAR)。ADC的作用机制 (图2) 是通过抗体部分特异性地识别并结合到目标细胞表面的抗原, 随后通过内吞作用进入细胞内部。在细胞内, ADC经溶酶体作用后连接子断裂, 释放出细胞毒素, 这些毒素能够结合至微管蛋白、DNA或拓扑异构酶, 进而诱导细胞死亡。同时, 部分ADC可以与内吞体的新生儿Fc受体 (neonatal Fc receptor, FcRn) 结合, 导致ADC循环至细胞外。一些疏水性小分子毒素还可通过细胞扩散,

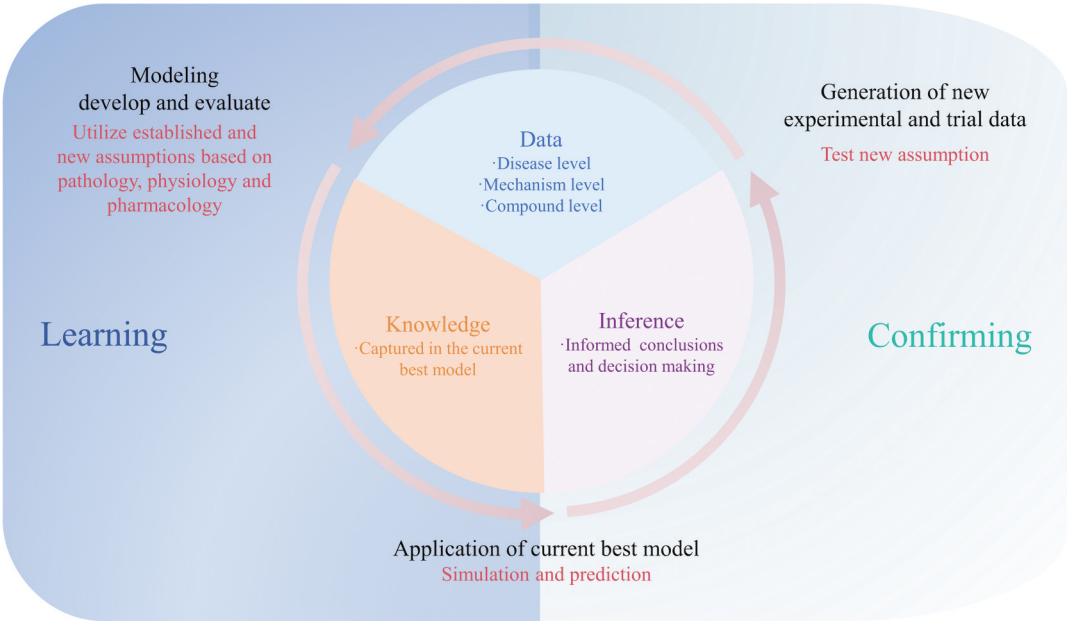

Figure 1 A quantitative framework flow of "Learn and Confirm Cycle". Image adapted with permission from reference[13]. Copyright © John Wiley and Sons Ltd.

对邻近肿瘤细胞产生杀伤活性, 称为旁观者效应[21]。

ADC 的分子设计使其同时结合了单克隆抗体药物和小分子毒素药物两者的 PK 和 PD 特征。ADC 通常经过静脉给药, 从分子量大小和空间体积来看, 小分子毒素药物的相对分子质量为裸抗体的 1/150。因此, ADC 表现出了诸多与抗体药物类似的 PK 特征, 如靶点介导的药物清除、FcRns 受体循环作用及非特异性蛋白酶降解等。然而, ADC 在代谢和清除途径过程中同时具有抗体药物和小分子毒素特征, 即在低剂量时呈非线性, 高剂量时呈线性。ADC 进入体内后, 小分子毒素通过酶解或化学反应逐渐从 ADC 药物上解离下来, 进一步增加了 ADC 药物在体内的复杂性, 导致在进行 PK 研究时需要对大量的分析物进行分析检测, 例如总抗体浓度、结合抗体浓度、游离小分子浓度等, 以便更好地了解 ADC 药物的体内过程[22-25]。

因此, ADC 药物的 PK/PD 之间的关系不仅需要综合考虑各种组成成分 (抗体、连接子和小分子毒素) 的特征, 还需要考虑它们之间的相互作用。ADC 的 PK 特征取决于抗体和小分子毒素在体内的动态变化, PD 特征通常涉及 ADC 与作用靶细胞之间的相互作用程度及其产生的效应。PK/PD 整合分析有助于理解 ADC 在体内的行为, 评估药物浓度与疗效和毒性之间的关系, 为临床决策提供科学依据。

2 MIDD 在 ADC 领域的应用

截至目前, 已有不少学术机构及医药公司发表了与 ADC 药物相关的模型研究案例 (表 2)[26-66]。通过整合在研发过程中生成的数据, 研究者们构建了数学模型框架来解决各个研发阶段的目标和问题。随着 M&S 技术的进步, 这些模型研究不仅仅依赖于传统的经验/机械模型, 同时还结合了 ADC 的作用机制及其在肿瘤内的分布特征进行建模 (图 3)[67]。下文通过将 MIDD 在 ADC 研发及临床阶段已有的应用参考案例归纳为分子筛选及设计优化、加速临床转化、评价药物–药物相互作用 (drug-drug interaction, DDI) 及临床剂量探索及优化。

2.1 分子筛选及设计优化

在药物研发的早期阶段, 筛选和优化适合临床研究的 ADC 分子是关键任务。为了更高效地完成这一任务, 研究人员需设计和开发合适的模型, 并确保将模型输出结果有效地分享给团队成员, 这对于药物研发的决策制定具有重大意义。

Maass 等[33]构建了描述 ADC 细胞水平作用机制 PK 模型, 该模型纳入了可能影响 ADC 在细胞内处理和有效载荷释放的相关参数。同时基于流式细胞术和荧光成像法对关键参数建立了定量方法, 如抗体与抗原的结合和解离常数、ADC 内吞速率和降解速率等。通过比较不同参数设置下细胞内释放的小分子毒素药物的曲线下面积 (AUC) 变化进行敏感性分析, 有助于了解细胞内处理步骤与设计参数之间的相互影响。结果表明 ADC 的内吞速率和小分子毒素药物的外排速率是影响药物在细胞中暴露量关键因素。Wada 等[30]

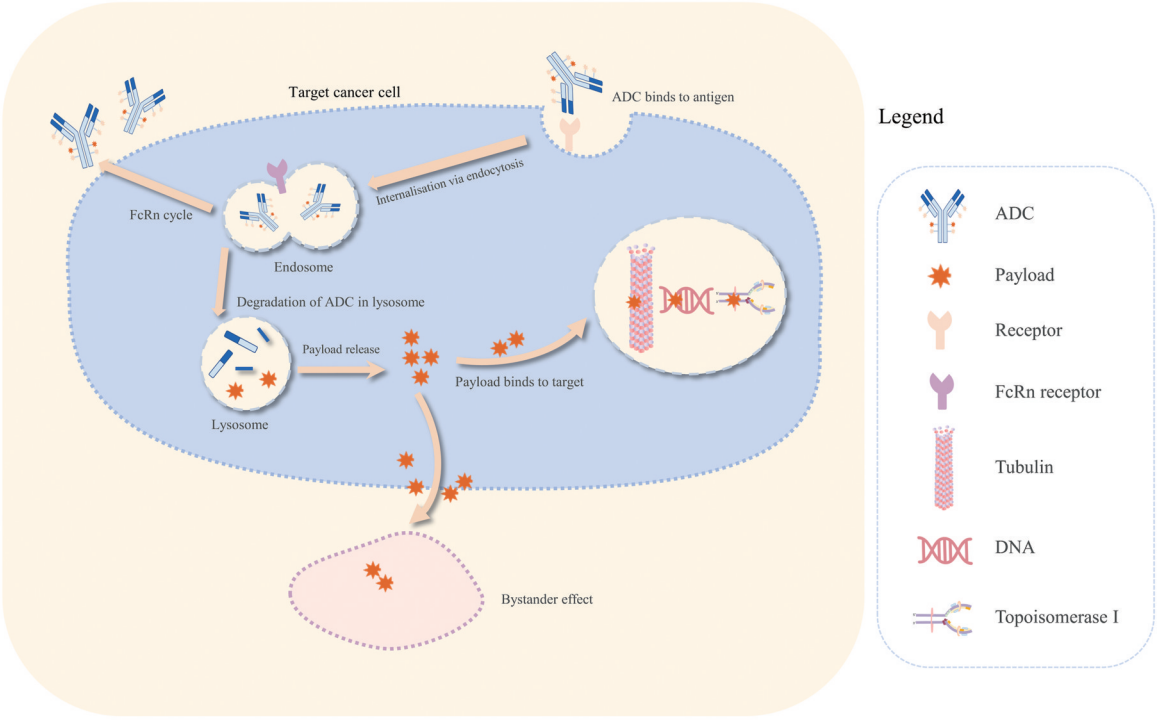

Figure 2 Mechanism action of antibody drug conjugates. FcRn: Neonatal Fc receptor

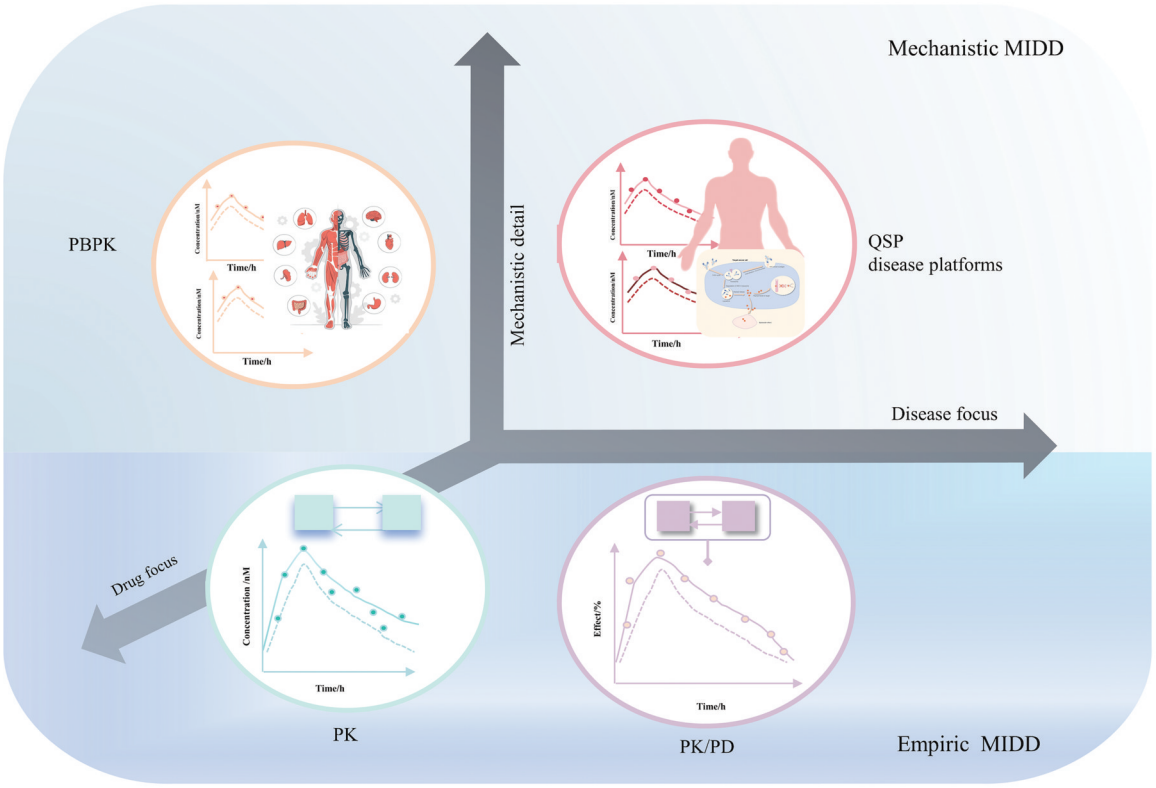

Figure 3 Schematic overview of model informed drug development approaches of ADC. MIDD: Model informed drug development

Table 2 List of prominent models for ADC. PK: Pharmacokinetics; PD: Pharmacodynamics; Pop-PK: Population pharmacokinetics; E-R: Exposure-response; PBPK: Physiologically based pharmacokinetic; QSP: Quantitative systems pharmacology; IVIVC: *In vitro-in vivo* correlation; DDI: Drug-drug interaction; MMAF: Monomethyl auristatin F; STEAP1: Six-transmembrane epithelial antigen of the prostate

Model	ADC-modeled	Data source	Reference
Bench to bedside translation of ADC using a multiscale mechanistic PK/PD model: a case study with brentuximab-vedotin	Brentuximab-vedotin	*In vitro*/*in vivo*/clinical	[26]
On translation of ADC efficacy from mouse experimental tumors to the clinic: a PK/PD approach	T-DM1 and 5T4-mc-MMAF	*In vivo*/clinical	[27]
A priori prediction of tumor payload concentrations: preclinical case study with an auristatin-based anti-5T4 ADC	5T4-mc-MMAF	*In vitro*/*in vivo*	[28]
A mechanistic PK model elucidating the disposition of T-DM1, an ADC for treatment of metastatic breast cancer	T-DM1	*In vivo*	[29]
Mechanistic PK/PD modeling of *in vivo* tumor uptake, catabolism, and tumor response of trastuzumab maytansinoid conjugates	T-DM1 and T-SPP-DM1	*In vitro*/*in vivo*	[30]
A mechanistic tumor penetration model to guide ADC design	General ADC	*In vitro*/*in vivo*	[31]
PBPK modeling as a tool to predict drug interactions for ADC	ADC based vc-MMAE	*In vivo*/clinical	[32]
Determination of cellular processing rates for a trastuzumab-maytansinoid ADC highlights key parameters for ADC design	Trastuzumab-maytansinoid	*In vitro*	[33]
Evolution of ADC tumor disposition model to predict preclinical tumor PKs of T-DM1	T-DM1	*In vitro*/*in vivo*	[34]
Preclinical to clinical translation of ADCs using PK-PD modeling: a retrospective analysis of inotuzumab ozogamicin	Inotuzumab ozogamicin	*In vitro*/*in vivo*/clinical	[35]
Multiscale modeling of ADCs: connecting tissue and cellular distribution to whole animal PKs and potential implications for efficacy	T-DM1	*In vitro*/*in vivo*	[36]
Quantitative characterization of *in vitro* bystander effect of ADC	Trastuzumab-vc-MMAE	*In vitro*	[37]
Development and translational application of an integrated, mechanistic model of ADC PKs	anti-STEAP1-vc-MMAE	*In vitro*/*in vivo*/clinical	[38]

Continued

Model	ADC-modeled	Data source	Reference
Application of a PK/PD modeling and simulation-based strategy for clinical translation of ADCs: a case study T-DM1	T-DM1	*In vivo*/clinical	[39]
A mechanism-based PK/PD model for hematological toxicities induced by ADCs	Brentuximab vedotin and T-DM1	*In vivo*	[40]
Pop-PK of brentuximab vedotin in patients with CD30-expressing hematologic malignancies	Brentuximab vedotin	Clinical	[41]
Measurement and mathematical characterization of cell-level PKs of ADCs: a case study with trastuzumab-vc-MMAE	Trastuzumab-vc-MMAE	*In vivo*	[42]
Platform model describing PK properties of vc-MMAE ADC	ADC based vc-MMAE	Clinical	[43]
Development of a translational PBPK model for ADC: a case study with T-DM1	T-DM1	*In vitro*/*in vivo*/clinical	[44]
Computational transport analysis of ADC bystander effects and payload tumoral distribution: implications for therapy	Trastuzumab-vc-MMAE and T-DM1	*In vitro*/*in vivo*	[45]
Establishing IVIVC for ADC efficacy: a PK/PD modeling approach	19 different ADCs	*In vitro*/*in vivo*	[46]
A "dual" cell-level systems PK-PD model to characterize the bystander effect of ADC	Trastuzumab-vc-MMAE	*In vitro*	[47]
A cell-level systems PK/PD model to characterize *in vivo* efficacy of ADCs	Trastuzumab-vc-MMAE	*In vitro*/*in vivo*	[48]
PK/PD modeling to support the re-approval of gemtuzumab ozogamicin	Gemtuzumab ozogamicin	Clinical	[49]
Antibody coadministration as a strategy to overcome binding-site barrier for ADCs: a quantitative investigation	Trastuzumab-vc-MMAE and T-DM1	*In vitro*/*in vivo*	[50]
An agent-based systems pharmacology model of the ADC kadcyla to predict efficacy of different dosing regimens	T-DM1	*In vitro*/*in vivo*	[51]
Evaluation of quantitative relationship between target expression and ADC exposure inside cancer cells	Trastuzumab-vc-MMAE	*In vitro*	[52]
PBPK model-informed drug development for polatuzumab vedotin: label for DDI without dedicated clinical trials	Polatuzumab vedotin	*In vitro*/*in vivo*/clinical	[53]
Pop-PK of brentuximab vedotin in adult and pediatric patients with relapsed/refractory hematologic malignancies: model-informed hypothesis generation for pediatric dosing regimens	Brentuximab vedotin	Clinical	[54]
Evolution of the systems PK-PD model for ADCs to characterize tumor heterogeneity and *in vivo* bystander effect	Trastuzumab-vc-MMAE	*In vitro*/*in vivo*	[55]
Mechanistic modeling of intra-tumor spatial distribution of ADC: insights into dosing strategies in oncology	General ADC	*In vivo*/clinical	[56]
Pop-PK of trastuzumab deruxtecan in patients with HER2-positive breast cancer and other solid tumors	T-Dxd	Clinical	[57]
E-R relationships in patients with HER2-positive metastatic breast cancer and other solid tumors treated with trastuzumab deruxtecan	T-Dxd	Clinical	[58]
Pop-PK of belantamab mafodotin, a BCMA-targeting agent in patients with relapsed/refractory multiple myeloma	Belantamab mafodotin	Clinical	[59]
Simulating the selection of resistant cells with bystander killing and antibody co-administration in heterogeneous HER2-positive tumors	Trastuzumab-vc-MMAE and T-DM1	*In vitro*/*in vivo*	[60]
Towards a platform QSP model for preclinical to clinical translation of ADCs	T-DM1and T-Dxd	*In vitro*/*in vivo*/clinical	[61]
PK and PD of ADC administered *via* subcutaneous and intratumoral routes	Trastuzumab-vc-MMAE	*In vivo*	[62]
Pop-PK of patritumab deruxtecan in patients with solid tumors	Patritumab deruxtecan	Clinical	[63]
Development of a generalized PK model to characterize clinical PK of MMAE-based ADCs	MMAE based ADC	*In vivo*/clinical	[64]
Quantitative evaluation of trastuzumab deruxtecan PK and PD in mouse models of varying degrees of HER2 expression	T-DXd	*In vitro*/*in vivo*/clinical	[65]
Optimizing solid tumor treatment with ADC using agent-based modeling: considering the role of a carrier dose and payload class	T-DM1 and T-Dxd	*In vitro*/*in vivo*	[66]

通过PK/PD模型比较了两种不同连接子的ADC在肿瘤内小分子毒素浓度及肿瘤药效方面的差异性。模拟结果表明, 连接子的不同会影响小分子毒素的释放特性, 连接子为二硫键的T-SPP-DM1比连接子为硫醚键的trastuzumab emtansine (T-DM1) 可能具有更快的小分子毒素释放特性, 这可能导致肿瘤内细胞毒性药物

的浓度更高。Shah等[46]开发了一种基于19种不同ADC药物的PK/PD模型, 并通过肿瘤静态浓度 (tumor static concentration, TSC) 建立体外−体内相关性 (*in vitro-in vivo* correlation, IVIVC)。模拟结果表明, 这些ADC药物在体内的TSC与体外的TSC呈线性正相关。因此, 这种合理的IVIVC方法能够利用体外药效数据来预测体内药效情况, 为体内药效实验设计提供参考。Singh等[37]开发了用以表征ADC的旁杀伤效应的体外PD模型, 该模型结合了两种不同的细胞分布模型来反映共培养系统中抗原高表达和低表达的细胞群体。这项研究提供了一个定量旁杀伤效应的框架, 有助于筛选出具有最佳旁杀伤能力的新型ADC。Ait-Oudhia等[40]基于T-DM1和Brentuximab vedotin开发了评估ADC血液毒性的PK/PD模型。模型模拟结果表明, 小分子毒素的释放速率是影响ADC血液学毒性的一个关键因素, 因此调整小分子毒素释放速率是改善血液毒性, 优化ADC治疗窗口的有效途径。

MIDD不仅对影响ADC药物性能的多个因素进行了参数化定量分析, 而且还利用有限的数据为药物分子的筛选和优化提供了独特的见解。即借助模型预测, 研究人员能够在早期阶段掌握不同结构组合 (如连接子稳定性、抗体内吞速率、小分子毒素外排效率及血液毒性等)对药物疗效与安全性的影响, 为更有效地筛选和优化ADC药物设计提供不同路径, 进而发掘更安全有效的药物分子。

2.2 加速临床转化 如何正确地转化临床前的研究结果, 预测临床疗效, 以提高临床转化成功率一直是ADC开发过程中面临的挑战。较低的临床成功率的主要原因之一在于难以将临床前的E-R关系正确地转化应用于临床中。此外, ADC药物具有复杂的作用机制及PK行为, 肿瘤组织中的药物浓度与血浆中的药物浓度在大多数情况下呈现不平衡状态, 肿瘤对ADC的摄取量并不等于其发挥疗效的药量。因此, 如果仅依赖传统经验模型来推测ADC药物浓度与疗效之间的关系可能并不可靠, 临床前和临床肿瘤生长抑制 (tumor growth inhibition, TGI) 的结果存在较大的差异。因此, 开发合理的模型用以描绘ADC肿瘤内暴露量与疗效之间的关系并转化到临床是临床前研究的核心任务。

Shah等[26]首次建立了基于brentuximab vedotin的机制PK/PD模型, 该模型描述了ADC在全身暴露过程并纳入了关键肿瘤生物指标 (如肿瘤大小、抗原表达水平及抗原内化等), 同时成功地基于临床前的研究对药物的临床效果进行了预测。基于这一模型基础, Singh等[39]等进一步开发了基于机制PK/PD模型转化ADC临床前至临床的通用策略, 并在T-DM1的研发过程中进行验证。首先, 该策略根据T-DM1临床前荷瘤小鼠研究建立肿瘤处置PK/PD模型; 随后, 将食蟹猴的PK参数通过异速放大至人体, 以预测药物在人体的PK行为; 最后将预测的人体PK数据、小鼠PK/PD模型估算的疗效参数与临床上观察到的乳腺癌体积和生长参数结合, 转化为人体临床PK/PD模型。最后, 该研究利用转化后的PK/PD模型, 进行了临床试验模拟, 即预测了T-DM1的无进展生存率 (progression-free survival, PFS) 和客观缓解率 (objective response rate, ORR)。模型模拟的人类表皮生长因子受体2 (human epidermal growth factor receptor 2, HER2) 1+和3+人群的PFS率结果与三个不同临床试验中观察到的相当。Scheuher等[61]建立了一个多尺度的QSP模型, 更多的机制细节被纳入模型。该模型使用T-DM1和trastuzumab deruxtecan (T-Dxd) 进行模型的开发、校准和验证。该模型与上述Singh等[39]的临床转化策略相似, 但融入了更详细的机制性描述, 如FcRn介导的抗体循环。它同样描述了ADC、抗体和小分子毒素在肿瘤内外的处置情况, 包括与肿瘤外部的目标结合。该模型被转化为人类, 并进行了虚拟临床试验模拟, 成功地预测了T-DM1和T-DXd在HER2阳性转移性乳腺癌治疗中的PFS反应, 包括基于HER2抗原表达差异的疗效区别。总的来说, 该模型是向ADC的平台QSP模型和策略迈进的一步, 它整合了多种类型的数据和知识来预测ADC的疗效。

这些研究提供了一个经过验证、可重复的临床转化策略 (图4), 它不仅成功整合了临床前和临床数据, 还能通过模拟不同给药方案来预测临床试验的结果。这一策略为其他ADC的临床转化研究提供了重要参考。

2.3 评价DDI DDI是指在使用两种或两种以上药物时, 由于药物之间的相互作用或与机体的反应,导致药物的效果、持续时间或性质发生不同程度的改变的现象。在考察ADC的DDI时需要考虑大分子抗体及小分子毒素药物的相互作用。虽然ADC的抗体部分与细胞色素P450同工酶 (CYP450) 的关联较小, 但其降解产物中的游离小分子毒素, 如monomethyl muristatin E (MMAE) 可能会被CYP和转运蛋白代谢和排泄。研究表明, MMAE既是CYP3A和P-糖蛋白的底物, 也是CYP3A的抑制剂。尽管循环中未结合的MMAE水平较低, 但由于其具有高活性和低暴露量的特性, 其DDIs仍可能通过调节重要消除途径发生。因此, 评估与游离小分子毒素药物相关的DDI潜力是支持ADC临床开发的重要风险内容。Chen等[32]首次通

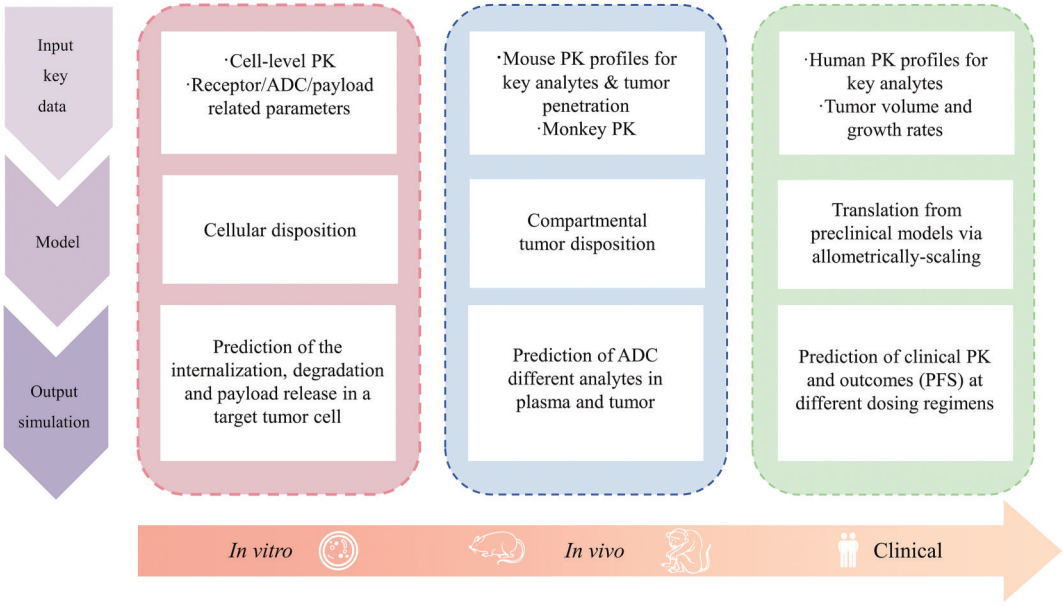

Figure 4 ADC clinical translational modeling and simulation strategy. PFS: Progression free survival

过PBPK模型对含有vc-MMAE的ADC进行DDI预测评估。该模型结合“自上而下”和“自下而上”两种建模方法, 利用抗CD22-vc-MMAE的临床前和临床数据进行建模。在确认相关参数后, 预测brentuximab vedotin的PK中MMAE的暴露量, 并将其与brentuximab vedotin的临床试验PK中MMAE暴露量进行比较和验证。最后通过验证模型预测brentuximab vedotin与咪达唑仑 (CYP3A底物)、酮康唑 (CYP3A抑制剂) 和利福平 (CYP3A诱导剂) 之间的DDI, 其AUC及药物最大浓度结果均与临床DDI研究观测值接近。研究还表明, 对于具有相同连接子 (vc) 及相同的小分子毒素 (MMAE) 的ADC, 无论单克隆抗体部分的设计如何, 其PK特征都相似。Samineni等[53]进一步优化了上述PBPK模型, 并成功将其应用于预测polatuzumab vedotin (CD79b-vc-MMAE) DDI的风险结果。此外, 该模型的预测成果已成功获得监管部门的认可, 它不仅能够有效替代传统的临床药物DDI试验, 还为药物说明书的编写提供了科学的指导依据。

2.4 临床剂量探索及优化 ADC设计的初衷是将高活性小分子毒素药物与抗体结合, 以降低药物毒性并扩大治疗窗口。然而, 越来越多的临床数据显示, 与传统药物相比, ADC的治疗窗仍相对较窄。许多ADC药物因毒性过大或风险/获益比过高而在临床开发过程中受阻。关键临床试验的剂量探索及优化是影响ADC研发成功与否的重要因素之一, 若未进行充分的剂量探索, 可能导致上市的剂量并非最佳剂量, 无法为患者提供疗效最大化、安全性风险最小化的治疗, 甚至可能导致治疗失败和药物退市[68]。

Mylotarg (gemtuzumab ozogamicin, GO) 是全球首个经FDA批准上市用于治疗CD33阳性急性髓性白血病 (acute myeloid leukemia, AML) 的ADC药物。然而, 该药物在验证性III期试验中却未能获得明显的临床效益, 且出现了严重的肝损伤和高死亡率, 导致研究提前终止研究并于2010年撤市。尽管GO退出了市场, 但由于AML患者的结局持续不良, 人们仍对其保持浓厚的研究兴趣。随后, 使用不同给药方案 (Mylo-France-1、ALFA-0701及AML-19) 的临床试验结果发现, 通过增加给药频率以较低剂量给药 (分级剂量) 可以显著提高GO疗效, 同时降低毒性, 但这些试验缺乏PK数据。Fostvedt等[49]基于GO过去的8项临床研究数据, 通过PK/PD模型进行分析, 以支持这些新的给药方案的安全性和有效性。该研究通过成年患者数据进行Pop-PK建模, 预测关键III临床试验 (ALFA-0701) 中GO总抗体的暴露量; 随后通过模型描述预测的GO总抗体的暴露量与疗效及安全性之间的关系, 并桥接外推至儿童患者; 另外建立半机制模型预测不同治疗方案对血小板和粒细胞的抑制作用情况。模型模拟结果表明, 与最初治疗方案相比 (9 mg·m^{-2}, 第1和15天给药), 新的给药方案中GO (3 mg·m^{-2}, 第1、4和7天给药) 与阿糖胞苷和多柔比星联合化疗方案的临床效果最佳。根据以上结果, FDA于2017年重新批准了GO上市, 用于治疗新诊断和复发的成人AML患者以及2～17岁儿童患者的复发AML。

T-DXd成为首个获得FDA批准用于治疗非小细胞肺癌 (non-small cell lung cancer, NSCLC) 的ADC药物, 其剂量优化探索策略充分展现了MIDD的应用优

势。Yin等[57]的研究首次公布了T-DXd在HER2阳性转移性乳腺癌和其他实体瘤患者中的Pop-PK特征。这项研究涵盖了5个临床试验的患者数据 (n = 679), 探索了每三周一次 (Q3W) 给药方案在不同剂量水平 (0.8～8.0 mg·kg^{-1}) 下的情况。研究采用了隔室模型描述了人体血清中T-DXd和游离药物Dxd的变化, 并为后续的E-R分析估算了PK参数。此外, 评估相关协变量 (种族、年龄、肿瘤大小等) 对药物暴露的影响。研究结果表明, 除了体重和血清白蛋白水平有显著影响外, 其他协变量等对T-DXd和游离Dxd的暴露影响均不超过20%。随后, 该团队[58]通过两项临床试验患者数据 (DESTINY-Breast01和J101) 通过E-R分析进行随机剂量探索研究。分析结果表明, T-DXd的AUC与临床ORR之间存在显著的统计关联, 同时安全性终点与T-Dxd和游离Dxd的暴露显著相关。预测结果表明, 当T-DXd剂量从5.4 mg·kg^{-1} Q3W增加至6.4 mg·kg^{-1} Q3W时, ORR和不良反应事件均有所增加。该研究通过比较不同剂量下的获益/风险比, 为探究5.4 mg·kg^{-1} Q3W剂量方案的有效性和安全性提供了依据。这些成功的模型案例表明, 在ADC的临床试验中, 利用M&S进行临床剂量优化不仅有助于深入分析人体内暴露及安全有效性数据, 还能补充数据证据, 进而降低临床研究过程中的不确定性[69,70]。

3 结语与展望

近年来, M&S技术在定量理解ADC方面取得了快速发展, MIDD为ADC的开发提供了独特的价值。本文讨论了不同模型案例在ADC研发阶段的不同应用, 旨为MIDD在ADC领域的应用提供有益的参考和启示。这些模型案例通过整合多元化的数据和知识, 对ADC的特性实现精准捕捉。同时, 模型在进行连续的验证和优化后, 能够在“假设”场景中生成新的数据, 从而有效应对传统实验方法的挑战, 为ADC开发周期内的各项决策提供了关键的支持和指导。

虽然目前已开发多种模型应用于ADC的研发关键环节, 但MIDD在ADC领域的应用仍面临一系列挑战。例如, 在早期研发阶段, 高质量数据往往较为缺乏, 这可能导致的模型在预测结果方面存在偏差; 肿瘤异质性和微环境的复杂性会对ADC疗效产生影响, 但当前建模工作尚未完全充分体现这些因素; ADC的毒性建模需要更多的研究和数据支持, 这使得目前对ADC治疗指数的预测仍存在困难; ADC在免疫肿瘤学治疗的建模和定量预测仍需进一步探索[71]。此外, 随着ADC研发技术的不断进步, 下一代ADC可能会出现新的结构设计, 如多特异性抗体、非细胞毒性载荷和多载荷系统等, 现有模型需进行进一步发展和适应。因此, 研究者可以通过利用QSP、疾病进展等新型模型技术平台来持续优化和改进模型[72-74], 从而提高其准确性和实用性。另一方面, 随着研究者们利用M&S软件持续进行深度学习和数据积累, 有望出现专门针对ADC药物研发的模型预测功能模块。这不仅极大地简化模型开发流程, 还优化了模型参数的调整过程, 为ADC研发提供更有益的支持。

现阶段, 一些国外知名制药企业, 如基因泰克和辉瑞, 已经率先将M&S工具融入ADC的研发过程中, 极大地提高了研发效率。我国目前在ADC研发方面的活动已占据全球超过半数比例, 在研发市场上展示出充沛的活力和巨大的潜力。如果能构建以模型为基础的ADC研发模式, 并在研发初期就开始运用M&S工具, 有望充分挖掘MIDD在ADC研发中的巨大潜力, 进一步提升研发效率并节省研发资源。

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