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Mini-Review

Understanding the Chemical Characteristics of Payloads and the Expression of Tumor-Associated Antigens of ADCs in Clinical Development

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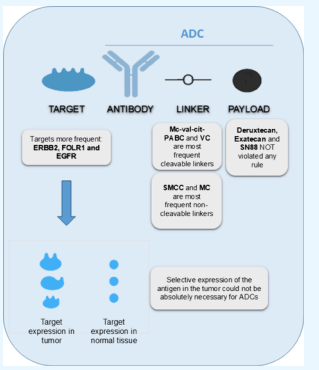
ABSTRACT: Antibody−drug conjugates (ADCs) have become one of the most promising therapeutic strategies for the treatment of cancer. This family of agents is composed of an antibody, a cytotoxic drug, and a linker that conjugates the drug to the antibody. The optimization of each component can potentially improve clinical activity and reduce the toxicity profile. In this article, we collected data from public sources regarding all ADCs that are currently in clinical development and extracted information for payload chemical characteristics, antibody, and linker type. In addition, we also evaluated data from genomic data sets to explore the expression of the tumor-associated antigen (TAA) in nontransformed tissue compared with the tumor. We evaluated 121 ADCs in clinical development. The most frequent targets included ERBB2, followed by FOLR1 and EGFR. 73% of ADCs used cleavable linkers, and only 14% were noncleavable, with 13% considered as undisclosed. While analyzing the physicochemical characteristics using established rules, we observed that 86% of the payloads violated the Lipinski rules, 11% violated Ghose rules, and 42% violated Brenk rules. Only three payloads did not violate any rule: deruxtecan, exatecan, and SN38, all from the camptothecin family. Regarding the conjugation type, only trastuzumab deruxtecan, labetuzumab govitecan, sacituzumab govitecan, BYON3521, and SYD1875 used homogeneous conjugation. An interesting observation was that for some ADCs, TAA expression was higher in normal tissue than in the tumor. In summary, our analysis highlights that only a limited number of ADCs incorporate payloads with favorable physicochemical properties and that several ADCs currently under development target TAAs with higher expression in normal tissues than in the corresponding tumors.



INTRODUCTION

Antibody-drug conjugates (ADCs) have demonstrated to provide meaningful clinical benefit, becoming one of the most promising novel therapeutic strategies in oncology.[1,2] Compared to other treatments, ADCs can selectively deliver cytotoxic agents or any other therapy to tumor cells.[3] This specificity is achieved through the use of monoclonal antibodies (mAbs) that selectively recognize tumor-associated antigens (TAAs) expressed on the surface of cancer cells, thereby enhancing the therapeutic index while minimizing systemic toxicity.[2,3] The first ADC approved was Gemtuzumab ozogamicin for Acute Myeloid Leukemia (AML) in 2000, which was later withdrawn and reapproved in 2017 with a different schedule. Other ADCs were approved later, including Brentuximab vedotin (BV) for Hodgkin lymphoma and systemic anaplastic large cell lymphoma, and trastuzumab emtansine (T-DM1) for HER2-positive breast cancer.[4] At present, there are more than 12 ADCs approved by regulatory agencies.[1,2,4]

An ADC is composed of three critical components: the monoclonal antibody, the cytotoxic drug, and the linker that conjugates the drug to the antibody.[5] The antibody confers specificity by binding to the TAA, the cytotoxic drug induces cell death upon internalization and release within the tumor cell, and the linker ensures the stability of the ADC in circulation and the controlled release of the drug in the tumor microenvironment.[5,6]

Despite the potential of ADCs, their therapeutic options are limited by several constraints. Challenges include the heterogeneous expression of target antigens, potential off-target and on-target off-tumor effects, and the development of resistance mechanisms by cancer cells.[7,8] Additionally, the

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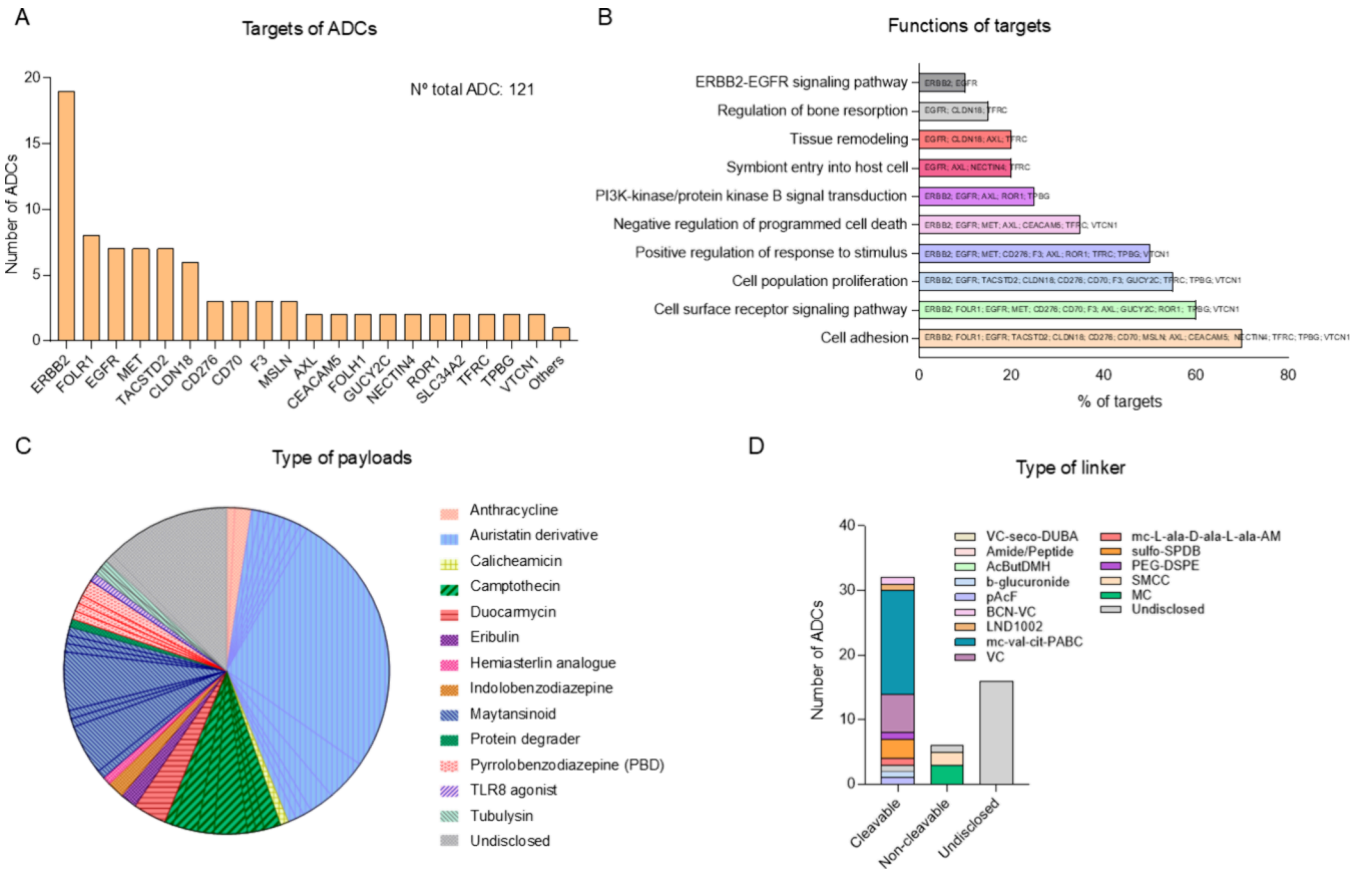

Figure 1. Analysis of ADCs in current clinical development. Information extracted using criteria from ref 12. (A) Number of ADCs that contain the specific targets following our research criteria. Other mean targets that have only one ADC. (B) Functions of the targets that have more than one ADC using g:Profiler. (C) Number of ADCs for each payload type. (D) Type of linkers from the ADCs studied.

stability of the linker and the efficacy of the payload are crucial factors that influence the overall effectiveness and safety profile of ADCs.[9]

In this context, one key strategy to enhance these therapies has been the identification of highly specific TAAs, aiming to minimize on-target off-tumor toxicity.[1] Identification of TAAs is a bottleneck in the development of ADCs, as high differential expression of the target in the tumor is considered mandatory for the successful development of this kind of agent.[10] In addition, linker optimization may facilitate controlled payload release, thereby enabling a bystander effect on neighboring cells that do not express the target TAA.[11] Of note, payload optimization has only recently been considered as a key avenue for improving ADC efficacy.[2] Indeed, our group has recently demonstrated that only two of the 12 approved ADCs employ payloads that can be regarded as having more favorable physicochemical properties.[2]

In this article, we evaluate the TAA specificity and the payload characteristics of all the ADCs currently under clinical development. We observed that several novel ADCs target TAAs that are also expressed in normal tissues, thereby raising concerns regarding tumor specificity. Furthermore, we confirmed that only a limited number of ADCs incorporate payloads with favorable physicochemical properties, underscoring this aspect as a critical area for further improvement.

MATERIALS AND METHODS

Search Criteria and Selection of the Studies. The list of approved ADCs and those under development in clinical studies was obtained from previously published articles, and our analysis was performed as a snapshot of the ADC field using the most recent data available up to July 2024.[12]

To identify the type of linker (cleavable or not) and the payload of each ADC, a literature search was performed on the peer-reviewed journal server https://www.adcreview.com/adc-drugmap/ and on PubMed, in the last case using the terms "ADC_name + payload" and/or "ADC_name + linker" (e.g., "SGN-15 payload" or "SGN-15 linker"). We selected the resulting articles, prioritizing those that included molecular representations of the payload's chemical structure.

Gene Functional Analysis and Drug Information. Analysis of biological functions from identified TAAs was performed using gene-set enrichment analysis, including g:Profiler with g:GOSt, and we selected Highlight driver terms in GO (most relevant terms of Gene Ontology).[13]

Information on approved compounds against identified TAAs was extracted from PanDrugs 2 (https://www.pandrugs.org/#!/)[14,15] and later confirmed directly at the FDA Web site.

Evaluation of Physicochemical Properties. All the physicochemical (PC) properties, including the Lipinski rule, were calculated using SwissADME, a software program available from the Swiss Institute of Bioinformatics.[16] In addition, each of the parameters that constitute the Lipinski rule was broken down. Also, the average calculation of the LogP and LogS parameters obtained by different algorithms in the software was included to highlight the lipophilicity and solubility of each payload.

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Table 1. Targets, Compounds, and Indications Where These Agents Have Received Regulatory Approval by the FDA

gene(s)	drug name	status description	therapy	family(ies)
EGFR	gefitinib	approved for lung cancer	small molecule	EGFR inhibitor (Cmap)
EGFR	vandetanib	approved for thyroid cancer	small molecule	EGFR inhibitor (Cmap)|RET tyrosine kinase inhibitor(Cmap)|VEGFR inhibitor(Cmap)
EGFR	sorafenib	approved for kidney, liver, and thyroid cancer	small molecule	FLT3 inhibitor (Cmap)|KIT inhibitor (Cmap)|PDGFR tyrosine kinase receptor inhibitor (Cmap)|RAF inhibitor (Cmap)|RET tyrosine kinase inhibitor (Cmap)|VEGFR inhibitor (Cmap)
EGFR|ERBB2	afatinib	approved for lung cancer	small molecule	EGFR inhibitor (Cmap)
EGFR	cetuximab	approved for colon, head and neck, and rectum cancer	antibody	other
MET	crizotinib	approved for lung cancer	small molecule	ALK tyrosine kinase receptor inhibitor (Cmap)
EGFR|ERBB2	dacomitinib	approved for lung cancer	small molecule	EGFR inhibitor (Cmap)
EGFR	erlotinib	approved for lung and pancreas cancer	small molecule	EGFR inhibitor (Cmap)
EGFR|ERBB2	lapatinib	approved for breast cancer	small molecule	EGFR inhibitor (Cmap)
EGFR	mereletinib	approved for lung cancer	small molecule	EGFR inhibitor (Cmap)
EGFR|ERBB2	neratinib	approved for skin cancer	small molecule	EGFR inhibitor (Cmap)
EGFR	panitumumab	approved for colon and rectum cancer	antibody	other
EGFR|ERBB2	trastuzumab	approved for breast, esophagus and stomach cancer	antibody	other
EGFR|ERBB2|MET	brigatinib	approved for lung cancer	small molecule	ALK tyrosine kinase receptor inhibitor (Cmap)|EGFR inhibitor (Cmap)
EGFR|ERBB2	zanubrutinib	approved for blood cancer	small molecule	Bruton's tyrosine kinase (BTK) inhibitor (Cmap)
MET	cabozantinib	approved for kidney, liver and thyroid cancer	small molecule	RET tyrosine kinase inhibitor (Cmap)|VEGFR inhibitor (Cmap)
MET	capmatinib	approved for lung cancer	small molecule	other
EGFR|MET	amivantamab	approved for lung cancer	antibody	other
EGFR	mobocertinib	approved for lung cancer	small molecule	other
ERBB2	tucatinib	approved for breast cancer	small molecule	EGFR inhibitor (Cmap)
MET	tivozanib	approved for kidney cancer	small molecule	VEGFR inhibitor (Cmap)
ERBB2	pertuzumab	approved for breast cancer	antibody	other
MET	tepotinib	approved for lung cancer	small molecule	hepatocyte growth factor receptor inhibitor (Cmap)
ERBB2	trastuzumab emtansine	approved for breast, esophagus, and stomach cancer	ADC	other
ERBB2	trastuzumab deruxtecan	approved for breast, esophagus and stomach cancer	ADC	other
MET	cabozantinib S-malate	approved for kidney, liver, and thyroid cancer	small molecule	RET tyrosine kinase inhibitor (Cmap)|VEGFR inhibitor (Cmap)
F3	tisotumab vedotin	approved for uterus cancer	ADC	other
NECTIN4	enfortumab vedotin	approved for bladder cancer	ADC	other
TACSTD2	sacituzumab govitecan [USAN]	approved for bladder and breast cancer	ADC	other
F3	tisotumab	approved for uterus cancer	antibody	other
NECTIN4	enfortumab	approved for bladder cancer	antibody	other
TACSTD2	sacituzumab	approved for bladder and breast cancer	antibody	other

ADCs can have cleavable or noncleavable linkers or be developed with either type. The molecular structure of the released payload, including any linker fragments or residual amino acids, was considered in ADMET parameter calculations. When available, both cleavable and noncleavable forms of the payload were included in these calculations. The binding type of the chemical structure of the ADCs was determined by searching scientific articles with the free portal of the National Library of Medicine (Pubmed) (https://www.ncbi.nlm.nih.gov/).

Gene Expression. RNA sequencing expression data to evaluate the transcriptomic levels of ADC TAAs in tumor and

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normal tissue were obtained from TCGA and GTEx (Genotype-Tissue Expression) databases,[17] using the bioinformatics tool 'Gene Expression Profiling Interactive Analysis' (http://gepia2.cancer-pku.cn/#index; last accessed on 15 July 2024).[18]

Statistical Analysis and Graphical Design. Bar charts, heatmaps, pie charts, and other graphics were depicted using GraphPad Prism 10.0.1 software (GraphPad Software, San Diego, CA, USA). The Venn diagram was represented through the web tool Bioinformatics & Evolutionary Genomics (https://bioinformatics.psb.ugent.be/webtools/Venn/).

Descriptive statistics were performed using GraphPad Prism 10.0.1 and Microsoft Excel 2016 software.

RESULTS

Description of ADCs in Current Clinical Development. A total of 121 ADCs were identified using our criteria as reported in the Materials and Methods section and published before.[12] The most frequent targets included ERBB2, followed by FOLR1 and EGFR, as displayed in Figure 1A.

The main functions of the TAAs presented in more than two ADCs included cell adhesion (70% of targets), cell surface receptor signaling pathway (60%), or cell proliferation (55%), among others (Figure 1B). We also analyzed which of these targets have approved treatments using the bioinformatic tool PanDrugs2, observing that F3, NECTIN4, TACSTD2, EGFR, ERBB2, and MET are currently being exploited as therapeutic targets (Table 1).

The family of payload most frequently identified included the auristatin derivative Maytansinoid, and Camptothecin (Figure 1C). Two payloads do not include chemotherapy-based entities and include Zuvotolimod (TLR8 agonist) and Smol006 (Protein degrader). The functions of these payloads include microtubule disruption, DNA intercalation, topoisomerase II inhibition, DNA alkylation, and vinca alkaloid–mediated inhibition, among others. Table 2 summarizes the complete list of payloads evaluated along with their mechanisms of action.

Regarding linker characteristics, 73% (*n*:88) of the linkers were cleavable and only 14% (*n*:17) were noncleavable. In 13% of the ADCs, data regarding the specific linker type were not disclosed. Among the cleavable linkers, the most frequently used was mc-val-cit-PABC, followed by VC, whereas for noncleavable linkers, the most common were SMCC and MC (Figure 1D). Of note, although literature data may allow inferences regarding whether a linker is cleavable or noncleavable, such assumptions remain speculative in the absence of full disclosure; therefore, we chose not to report them.

Physicochemical (PC) Characteristics of Payloads. To evaluate the PC characteristics, we used methods as described in the Materials and Methods section. These methods, classically used for the evaluation of oral absorption, can also be applied to the capacity of a compound to penetrate cellular membranes, as our group previously described.[2] Most of the payloads, 31 (86%), violated the Lipinski rules, with only 5 (14%) conforming to them. Furthermore, when considering other well-established rules, such as Ghose and Brenk, only 4 payloads (11%) and 15 payloads (42%), respectively, did not violate the rules (Figure 2A). Only three payloads did not violate any rule, and those included DXd, Exatecan (DX-8951), and SN38 (Figure 2 B). All these payloads belong to the Camptothecin family, which are inhibitors of the topoisomerase I (Figure 2C). Of note, two of them are already approved, including DXd and SN38, and they form part of two ADCs, Trastuzumab deruxtecan and Sacituzumab govitecan against ERBB2 (HER2) and TACTDS2 (TROP2), respectively. Among the nonapproved payloads was Exatecan

Table 2. List of Payloads Including Their Class and Mechanism of Action

class of payload	payload molecule	mechanism of action
anthracycline	doxorubicin	DNA intercalation
	PNU-159682	
auristatin derivative	AS269 (MMAF+PEG linker)	microtubule dysregulation
	auristatin F hydroxypropylamide (dolaflexin analog)	
	auristatin-0101	
	BAY1168650	
	duostatin 5	
	duostatin-5.2 (duostatin 5 analog undisclosed)	
	ixadotin	
	MMAE	
	MMAF	
	MMAF-HPA	
	PF-06380101 (Aur0101)	
	SHR152852	
	ugodotin	
calicheamicin	N-acetyl calicheamicin	double-stranded DNA breakages
camptothecin	AZ14170132	inhibition of topoisomerase II
	belotecan (Camptobell; CKD602)	
	SHR9265	
	DXd	
	exatecan (DX-8951)	
	SN38	
	Ed-04 (undisclosed)	
duocarmycin	DUBA	alkylation of DNA
eribulin	eribulin	microtubule dysregulation
hemiasterlin analogue	SC209	tubulin Inhibitor
indolobenzodiazepine	IGN-P1	alkylation of DNA
maytansinoid	batansine (undisclosed)	competitive inhibitor of vincristine
	DM1	
	DM21	
	DM21C	
	DM4	
	liposomic doxorubicin	
	M24	
	maytansine	
protein degrader	undisclosed (SMol006, CRBN PROTAC)	protein degrader
pyrrolobenzodiazepine (PBD)	pamozirine (PBD-dimer derivative, releases SG3199)	DNA intercalation
	PBD-dimer derivative	
	PBD-dimer derivative (unspecified)	
	tesirine (PBD-dimer derivative, releases SG3199)	
	tesirine (PBD-dimer derivative, releases SG3199)	
TLR8 agonist	zuvotolimod (motilimod derivative)	target inhibitor
tubulysin	TAM470	microtubule dysregulation
	tubulysin	
undisclosed	TAM (undisclosed)	
	undisclosed	

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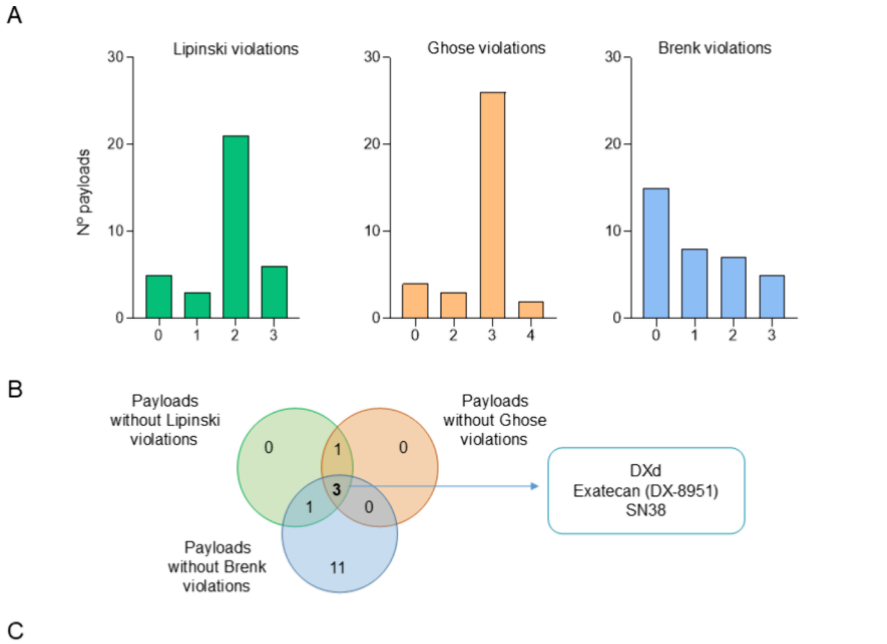

Payload	ADC	Target	Class payload	Linker
DXd	Datopotamab deruxtecan	TACSTD2	Camptothecin	Cleavable
	DS-3939a	MUC1		
	Ifinatamab Deruxtecan	CD276		
	Trastuzumab deruxtecan	ERBB2		
Exatecan (DX-8951)	Patritumab deruxtecan	ERBB3		
	PRO1184	FOLR1		
SN38	Labetuzumab govitecan	CEACAM5		
	Sacituzumab govitecan	TACSTD2		
	STI-3258 (ESG-401)	TACSTD2		

Figure 2. Physicochemical characteristics of payloads. (A) Number of payloads that violate or do not follow the rules of Lipinski, Ghose, and Brenk. The *X*-axis shows the number of violations. (B) Proportion of payloads without any violations. (C) Main characteristics of the payloads described in part B.

Table 3. Description of the Payloads without Lipinski's Violations Including the Name of the ADC, Target, Payload Class, and Linker

payload	Brenk violations	Ghose violations	ADC	target	class payload	linker
AZ14170132	1		AZD8205	VTCN1	camptothecin	cleavable
			AZD9592	EGFR-cMET		
DXd			datopotamab deruxtecan	TACSTD2		
			DS-3939a	MUC1		
			ifinatamab deruxtecan	CD276		
			trastuzumab deruxtecan	ERBB2		
exatecan (DX-8951)			patritumab deruxtecan	ERBB3		
			PRO1184	FOLR1		
SN38			labetuzumab govitecan	CEACAM5		
			sacituzumab govitecan	TACSTD2		
			STI-3258 (ESG-401)	TACSTD2		
DUBA		2	BYON3521	MET	duocarmycin	
			SYD1875	TPBG		
			SYD985	ERBB2		
			vobramitamab duocarmazine	CD276		

(DX-8951), which is incorporated in ADCs targeting ErbB3 and FOLR1.

DUBA, AZ14170132, DXd, Exatecan (DX-8951), and SN38 did not violate any Lipinski rules, but DUBA violated two Ghose rules and AZ14170132 violated one Brenk rule. These agents belong to the Camptothecin and Duocarmycin family (Table 3).

Site-Specific Conjugation of the Selected ADCs. We next examined the conjugation strategies of those ADCs whose payloads did not violate any of the Lipinski rules. Information on the search criteria is described in the Materials and Methods section. This information was lacking in 60% of ADCs. An important finding is that some of the identified ADCs used homogeneous conjugation, including Trastuzumab deruxtecan, Labetuzumab govitecan, Sacituzumab govitecan, BYON3521, and SYD1875.[19,20]

The ADC BYON3521 was generated through site-specific conjugation to cysteine residues, linking vc-seco-DUBA to the

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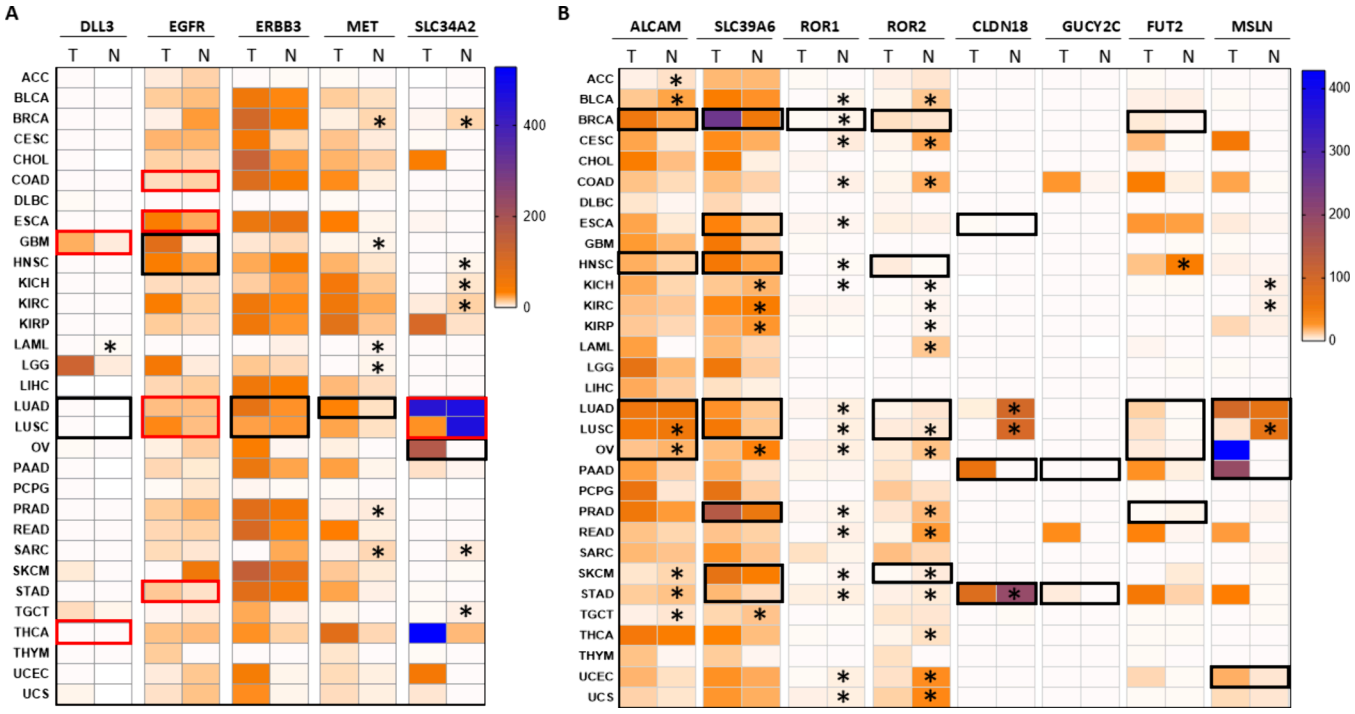

Figure 3. ADC targets nonimmunological expression in normal tissue (N) and tumor (T). (A) ADC targets studied in phase 3. (B) ADC targets studied in phase 2. Black boxes indicate tumors, where clinical trials are being conducted. The red boxes indicate the tumors in which clinical trials are currently being conducted 2. "*" points tumors where the expression of the target is higher in their corresponding normal tissue.

SYD2884 antibody, resulting in a drug-to-antibody ratio (DAR) of approximately 1.8.[21] SYD1875, a 5T4-targeting ADC was built by the conjugation of vc-seco-DUBA at HC-41C.[22]

In the case of Sacituzumab govitecan, Labetuzumab govitecan, and Trastuzumab deruxtecan, all were developed by the full reduction of interchain disulfides to link SN-38 and DXd to monoclonal antibodies against Trop-2 (Sacituzumab govitecan), CEACAM5 (Labetuzumab govitecan), or HER2 (Trastuzumab deruxtecan, respectively). This specific binding allowed a DAR of 8.[10,23]

Expression of TAAs in Nontumoral Tissue. We analyzed the expression levels of TAAs targeted by ADCs currently in phase 2 and phase 3 clinical trials, comparing their expression in tumors with that in the corresponding normal tissues. In phase 3 studies, five ADC TAAs: DLL3, EGFR, ERBB3, MET, and SLC34A2/NaPi2b, were identified in different tumor types (Figure 3A). None of them showed higher expression in normal tissue than in the tumor, where the phase 3 clinical trial is currently under development. However, SLC34A2/NaPi2b expression levels were higher in normal tissue (468.53 TPM and 461.78 Ps) than in Lung Adenocarcinoma (LUAD) (445.01 TPM) and Lung Squamous Cell (LUSC) (27.43 TPM), both tumors where a phase 2 trial is also underway for this ADC (Figure 3A).

Regarding ADCs studied in phase 2 clinical trials, we identified eight ADC TAAs: ALCAM, SLC39A6, ROR1, ROR2, CLDN18, GUCY2C, FUT2, and MSLN (Figure 3B). Among them, ALCAM expression levels were higher in normal tissue (48.45 TPM and 18.67) than in LUSC (44.46 TPM) and OV (14.01 TPM). In the same way, ROR1 and MSLN showed higher expression in normal tissue (2.12 TPM and 64.687 TPM, respectively) than in BRCA (1.08 TPM) and LUSC (5.23 TPM), respectively. The expression of ROR2 in LUSC (4.10 TPM) and SKCM (0.79 TPM) was lower than in their respective normal tissues (5.30 TPM and 4.04 TPM).

We then compared the expression of the TAAs with their expression in other nontransformed tissues. We observed that for some of them, the expression was higher in normal tissue than in the tumor type where the clinical trial was under development.

Both DLL3 and SLC34A2/NaPi2b, studied in a phase 3 clinical trial in LUSC and OV, respectively, showed higher expression in other normal tissues than in these tumors (Figure 4A). DLL3 expression was higher in nontransformed tissue of GBM, LAML, LGG, and TGCT (3,86 TPM, 0.91 TPM, 3.86 TPM, and 2.04 TPM, respectively) than in LUSC (0.35 TPM). Likewise, SLC34A2/NaPi2b showed a higher expression in nontransformed tissue of LUAD and LUSC (468.53 TPM and 461.78 TPM, respectively) than in OV (176.26 TPM).

Some ADCs studied in phase 2 clinical trials also showed higher expression in normal tissue than in the tumor type where the clinical trials are being conducted. We observed that ROR1 was more expressed in normal tissue (>1.08 TPM), such as bladder cancer (BLCA), Esophagus squamous carcinoma (CESC), or colon adenocarcinoma (COAD), among others, than in BRCA, which is the tumor type where the clinical trial is under development (Figure 4B). ROR2 expression levels were also more elevated (>4.1 TPM) in several normal tissues than in LUSC (Figure 4B). Similar results were observed with CLDN18 and FUT2.

DISCUSSION

Antibody-drug conjugates (ADCs) represent a cutting-edge therapeutic approach in oncology, combining the targeting capabilities of monoclonal antibodies (mAbs) with the potent cytotoxic effects of small-molecule drugs.[1]

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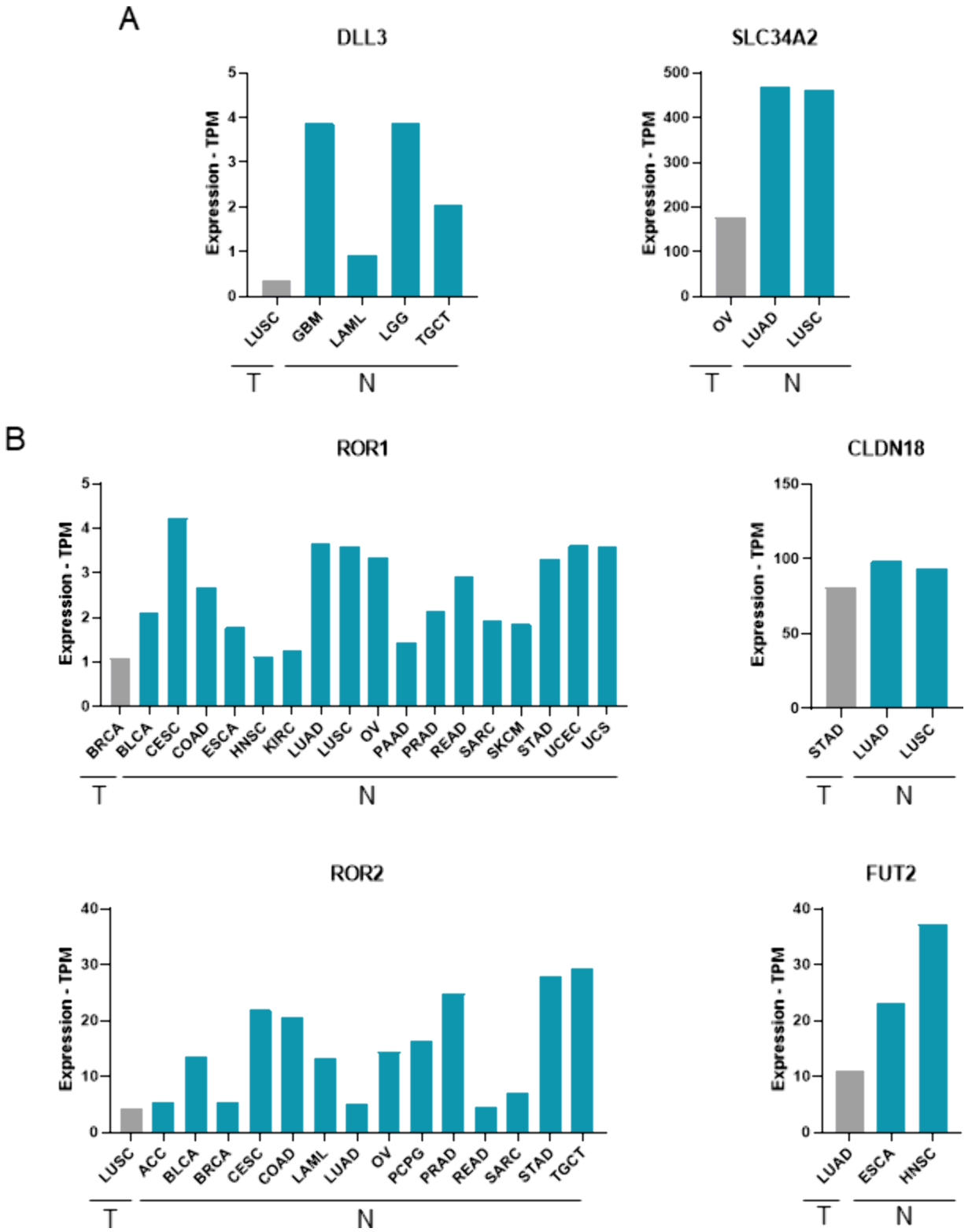

Figure 4. Expression levels of ADC-targeted TAAs in tumors undergoing clinical evaluation, compared with their expression in corresponding normal tissues. (A) ADC targets studied in phase 3 clinical trials. (B) ADC targets studied in phase 2 clinical trials.

In this article, we evaluate two parameters that can directly influence the activity of ADCs: payload characteristics and TAA expression.

The physicochemical properties of ADC payloads are crucial determinants of their therapeutic efficacy, affecting aspects such as stability, solubility, potency, and the ability to be conjugated to antibodies.[11] In this context, it has been suggested that those payloads with more adequate properties can diffuse easily through cellular membranes and produce a bystander effect.[24] This effect may influence clinical efficacy, particularly in cases of tumor heterogeneity or low TAA expression, which can act as mechanisms of resistance.[7] In a

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previous article, our group described that a minority of the approved ADCs display favorable payload physicochemical characteristics.[2] Typically, small molecules efficiently penetrate and internalize cellular membranes,[25,26] by contrast, larger payloads may have difficulties with tumor penetration.[2] In our study, we observed that novel payloads with improved physicochemical properties have been incorporated less frequently than desirable, highlighting a potential limitation in current ADC development that could impact both efficacy and safety. In this context, initiatives to design payloads with optimal properties are currently in preclinical research,[27] and it is expected that more ADCs with these characteristics will be incorporated soon.

The ability to efficiently conjugate the payload to the antibody can improve several of the ADC properties. In this context, the conjugation process should result in a stable, reproducible drug-to-antibody ratio (DAR).[11] Site-specific conjugation techniques, such as engineered cysteine residues or enzymatic conjugation, are often employed to ensure uniformity and stability of ADCs,[11,28] thereby improving the overall properties of the compound, although they do not fully guarantee enhanced safety or efficacy. Unfortunately, our analysis revealed that publicly available information on the conjugation types of ADCs in clinical development is very limited. Indeed, only Trastuzumab deruxtecan, Labetuzumab govitecan, Sacituzumab govitecan, BYON3521, and SYD1875 were identified as having homogeneous conjugation.

In our previous analysis, we found that the number of novel targets, including those representing new therapeutic opportunities (such as niche indications or cotargeting), was very limited, and we proposed potential mechanisms of resistance.[4,12] Here, we confirm in detail some of our previous observations.[12] In this article, we question the classical dogma regarding the specificity of the TAA as a minimum requirement for the development of an ADC. For instance, in some ongoing studies evaluating ADCs, TAA expression was higher in certain nontransformed tissues than in the corresponding tumors. In the case of SLC34A2/NaPi2b, expression in LUAD and LUSC, both tumors currently being evaluated in a phase 2 trial, is lower than in the corresponding normal tissues. Likewise, the expression levels of other ADC TAAs, such as ALCAM, ROR1, MSLN, and ROR2, were higher in normal tissue than in the respective tumor type where the clinical trial is being conducted. In addition, we observed similar results when comparing TAA expression in the tumor with that in other normal tissues. ADC-targeted TAAs, such as DLL3, CLDN18, and FUT2, among others, were more highly expressed in several nontransformed tissues than in the tumor types for which the clinical trials were conducted. These findings suggest that selective antigen expression in the tumor may not be strictly required for the development of an ADC.

Our study has several limitations. First, it is based on ongoing studies, and the data analyzed were obtained from publicly available sources. Second, certain information has not been disclosed, preventing a complete evaluation of aspects such as the linker conjugation type. Finally, TAA expression data were derived from gene expression databases, which may not fully reflect total protein expression.

We provide a snapshot (Figure 5) of more frequent ADCs that are currently in clinical development, including payload physicochemical characteristics, conjugation type, and TAA expression. We observed that a reduced number of ADCs use

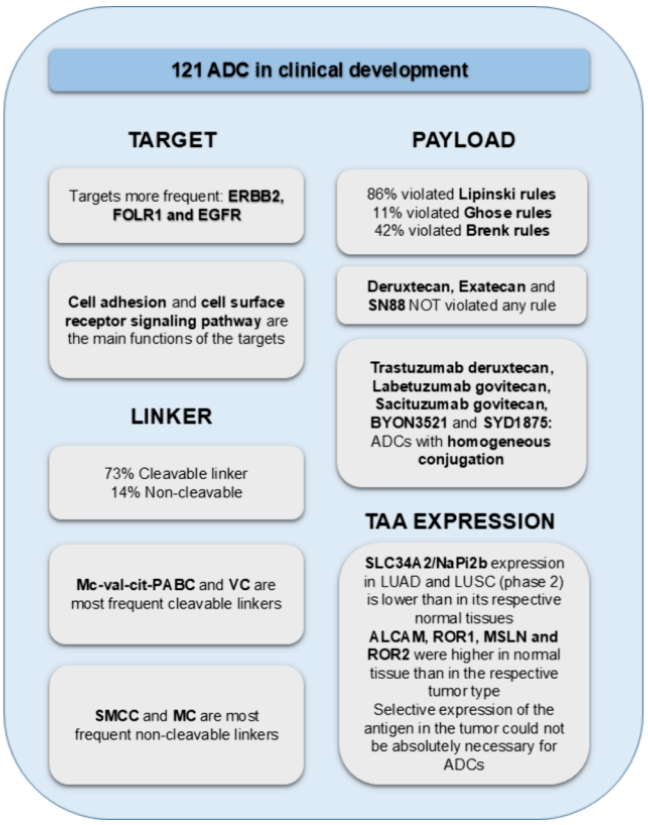

Figure 5. Graphical abstract. Antibody-drug conjugates (ADCs) have gained increasing attention as a promising strategy for the treatment of various cancers. The study assessed 121 ADCs in-depth, considering their structural biology, biochemistry, and pharmacology, antibody and linker composition, as well as the expression of tumor-associated antigens (TAAs) in tumor and normal tissues. Most of the ADCs were shown to utilize cleavable linkers, and only a handful used a payload with optimal physicochemical properties or homogeneous conjugation.

payloads with favorable physicochemical characteristics. Moreover, some ADCs are currently under development against TAA that are more expressed in normal tissue than in the selected tumor.

FUTURE OUTLOOK

Future ADC development should prioritize the design of payloads with optimized physicochemical properties, as our analysis revealed that more than 80% of those currently in clinical development violate established medicinal chemistry rules, with only camptothecin derivatives (DXd, Exatecan, SN38) displaying favorable profiles. Wider adoption of site-specific conjugation is also warranted, since only a handful of ADCs—such as trastuzumab deruxtecan, labetuzumab govitecan, sacituzumab govitecan, BYON3521 and SYD1875—currently use homogeneous strategies despite their potential to improve stability and pharmacokinetics. Equally important, antigen discovery pipelines must evolve to integrate transcriptomic and proteomic data, given our observation that several TAAs under clinical evaluation (e.g., SLC34A2/NaPi2b, ROR1, MSLN) are more highly expressed in normal tissues than in the tumors being targeted, challenging the paradigm of strict tumor selectivity. Incorporation of microenvironment-responsive linker chemistries and rational drug combinations is expected to further expand the therapeutic

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window and mitigate resistance. Together, these strategies will be essential to translate the next generation of ADCs into safer and more effective therapies across diverse cancer indications.

■ ASSOCIATED CONTENT

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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Notes

The authors declare no competing financial interest.

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Dr. Manuel Pedregal earned his medical degree from the University of Seville, completing part of his studies in Copenhagen. He trained in medical oncology at Fundación Jiménez Díaz, with research at Dana-Farber, and a master's degree in molecular oncology. In 2020, he became a consultant in the Gastro-Intestinal Unit running phase II/III trials. Since 2022, he has been a clinical investigator in the FJD-START Phase I Unit.

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Dr. Emiliano Calvo earned his medical degree and PhD in Spain and completed an Advanced Fellowship in Drug Development in Texas. He leads early-phase oncology research as the president of START Europe and INTHEOS and directs clinical research at START Madrid. He is a full professor at CEU San Pablo University and serves on numerous international oncology committees. With over 140 publications, his work focuses on immunotherapy and targeted cancer therapies.

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■ ABBREVIATIONS

ACCA,adrenocortical carcinoma; ADC,antibody–drug conjugate; ADMET,absorption, distribution, metabolism, excretion, and toxicity; BLCA,bladder urothelial carcinoma; BRCA,breast invasive carcinoma; BV,brentuximab vedotin; CESC,cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL,cholangiocarcinoma; COAD,colon adenocarcinoma; DAR,drug-to-antibody ratio; DLBC,lymphoid neoplasm diffuse large B-cell lymphoma; ESCA,esophageal carcinoma; FDA,Food and Drug Administration; GBM,glioblastoma multiforme; GTEx,genotype-tissue expression; HNSC,head and neck squamous cell carcinoma; KICH,kidney chromophobe; KIRC,Kidney renal clear cell carcinoma; KIRP,kidney renal papillary cell carcinoma; LAML,acute myeloid leukemia; LGG,brain lower grade glioma; LIHC,liver hepatocellular carcinoma; LUAD,lung adenocarcinoma; LUSC,lung squamous cell carcinoma; mAbs,monoclonal antibodies; MESO,mesothelioma; NSCLC,nonsmall cell lung cancer; OV,ovarian serous cystadenocarcinoma; PAAD,pancreatic adenocarcinoma; PBD,pyrrolobenzodiazepine; PC,physicochemical; PCPG,pheochromocytoma and paraganglioma; PRAD,prostate adenocarcinoma; READ,rectum adenocarcinoma; SARC,sarcoma; SKCM,skin cutaneous melanoma; STAD,stomach adenocarcinoma; TAA,tumor-associated antigens; TCGA,The Cancer Genome Atlas; T-DM1,trastuzumab emtansine; TGCT,testicular germ cell tumors; THCA,thyroid carcinoma; THYM,thymoma; TPM,transcripts per million; UCEC,uterine corpus endometrial carcinoma; UCS,uterine carcinosarcoma; UVM,uveal melanoma

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