



ANTIBODY-DRUG CONJUGATES

A landscape analysis of recent research advancement

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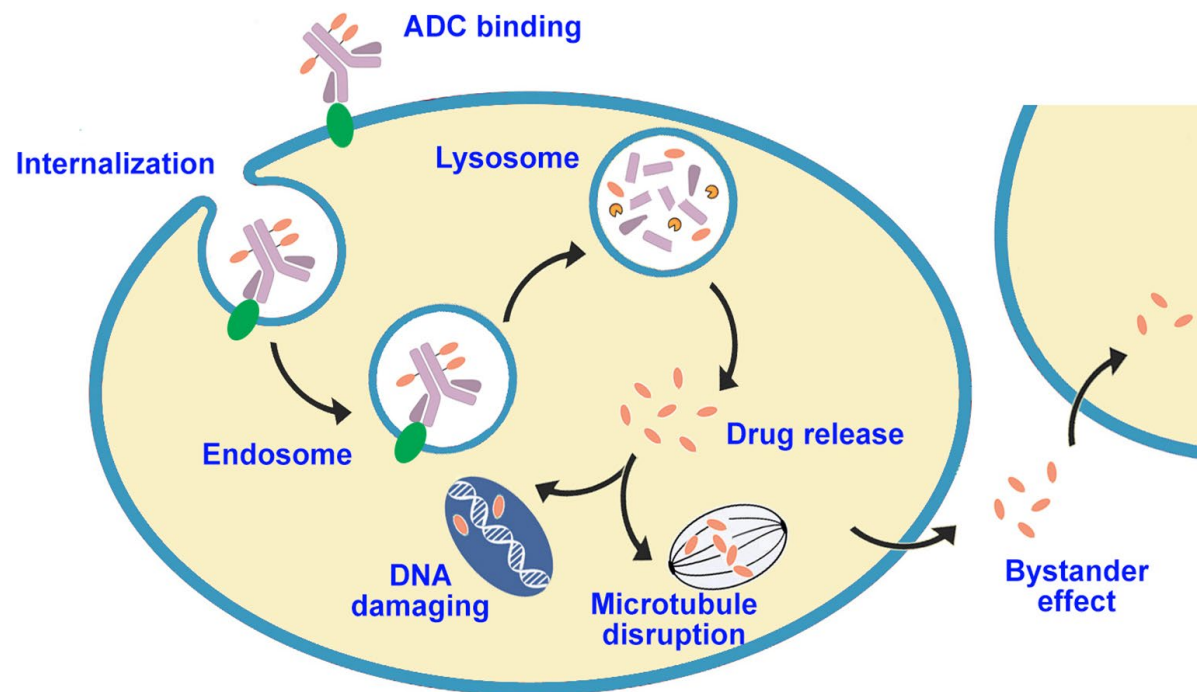
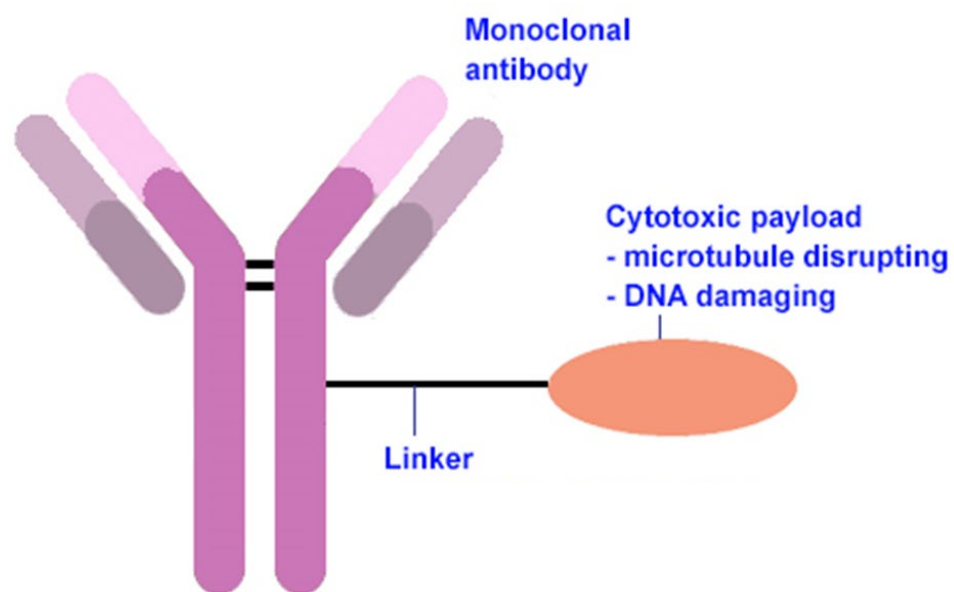
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What is an antibody-drug conjugate (ADC)?

Structure and mechanism of action

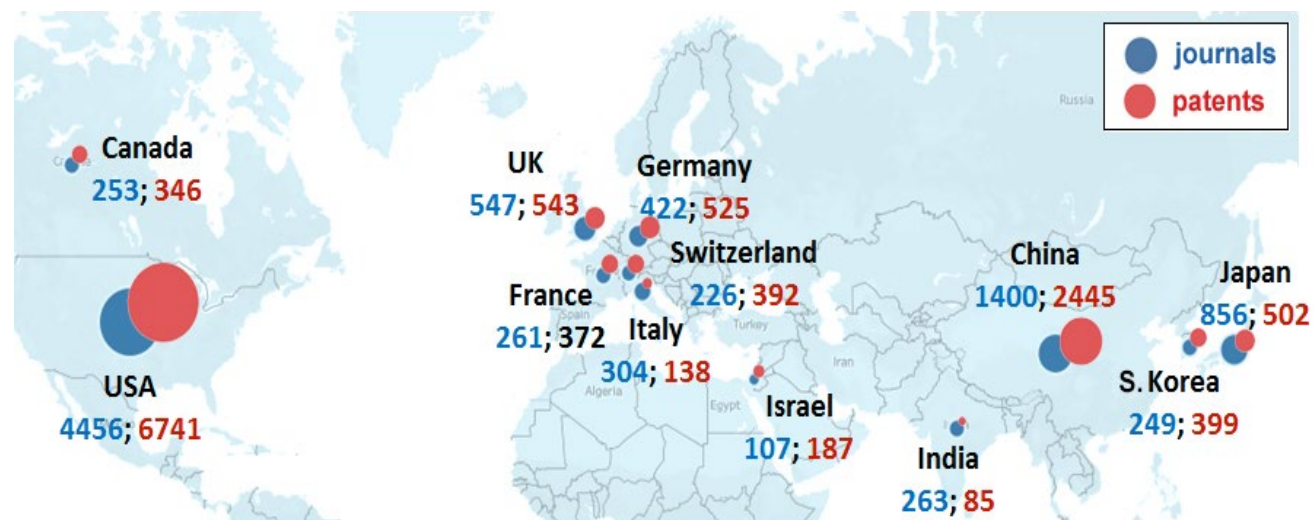
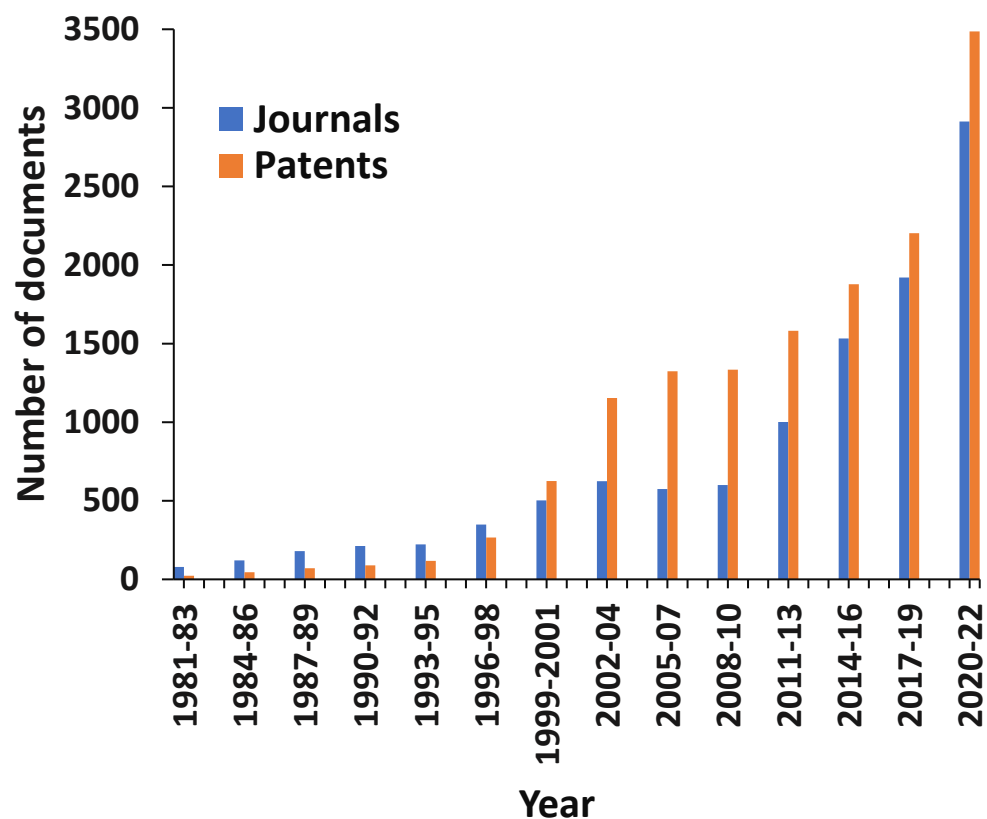


Challenges in ADC development



Growth of research publications

ADCs continue to be an active area of research and development



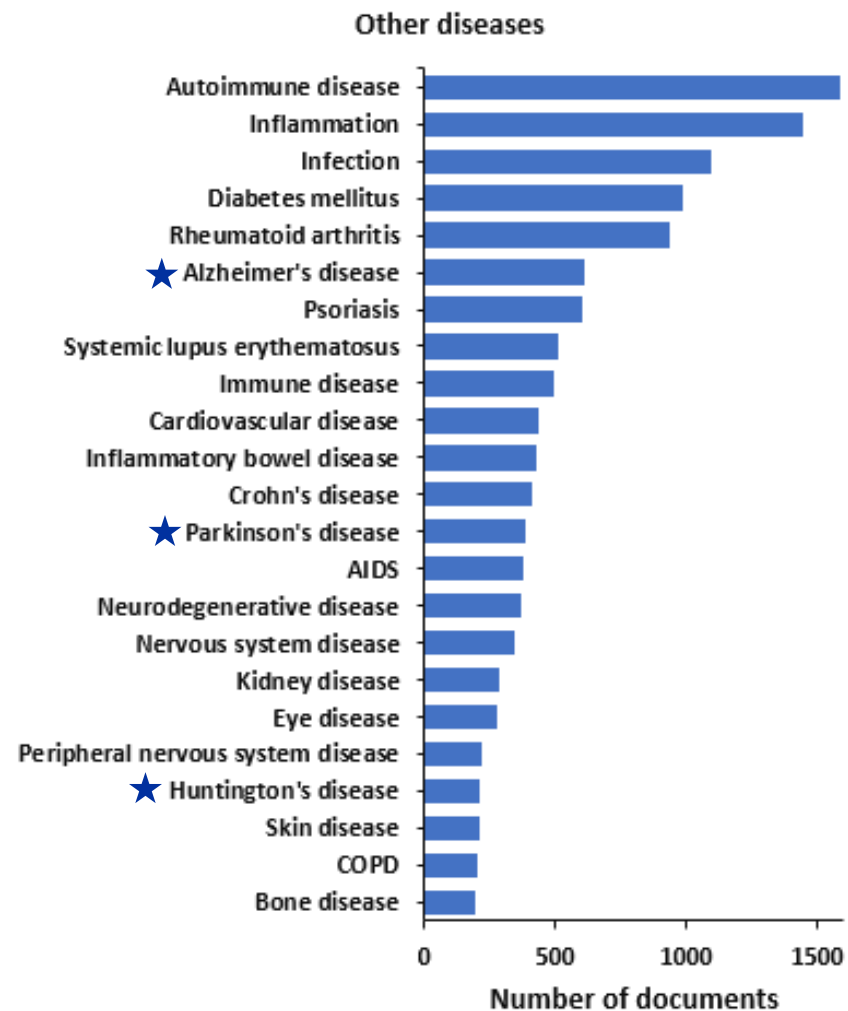
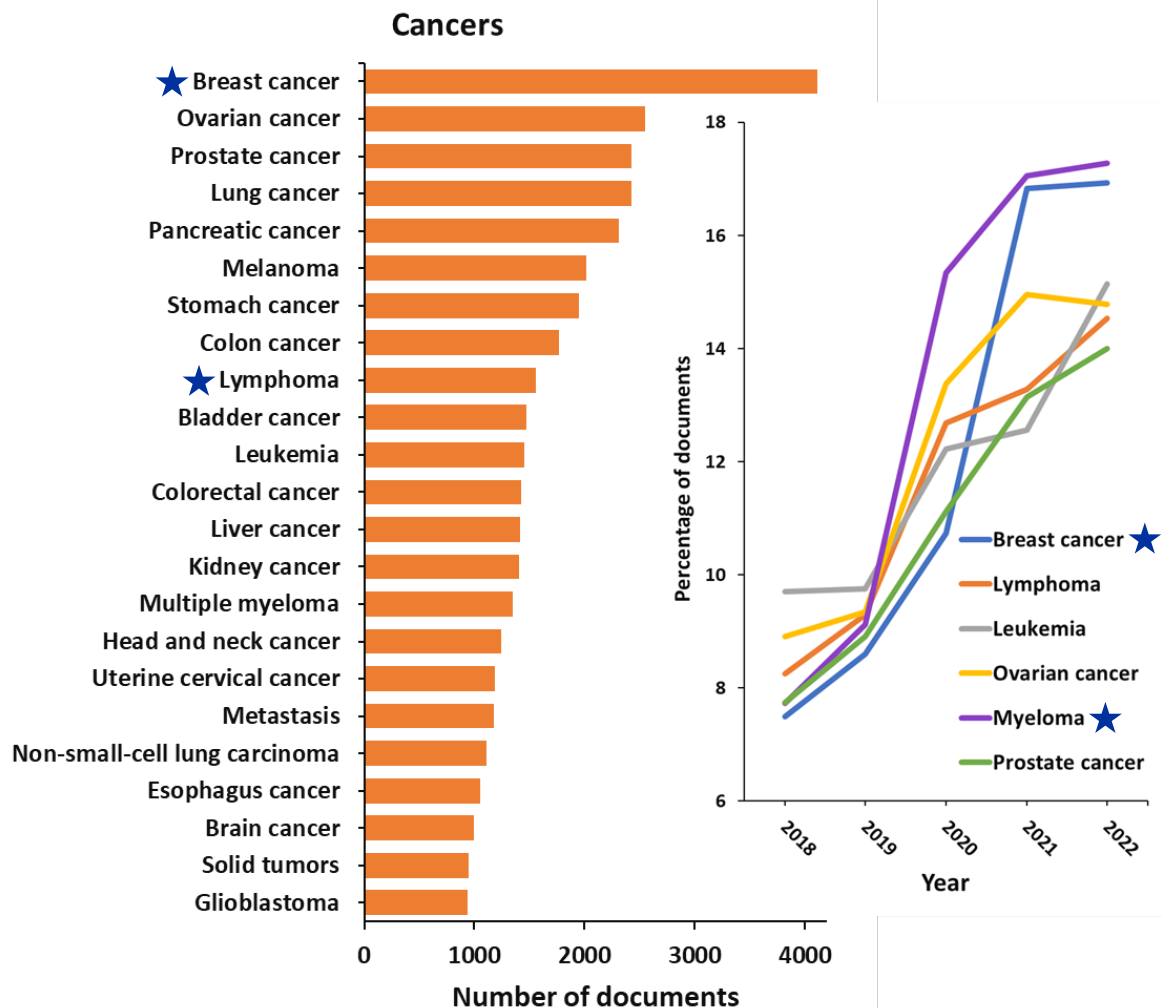
Organizations publishing on ADC-related technologies

Journal and patent activity dominated by commercial entities

Organization	No. Journal Articles	Assignee (Companies)	No. Patents	Assignee (Universities / Hospitals)	No. Patents
Genentech	155	Genentech	196	University of California	141
The Scripps Research Institute	87	Immunomedics	113	University of Texas	75
University of California	76	Regeneron Pharmaceuticals	100	US Dept. Health & Human Services	60
Chinese Academy of Sciences	58	Seattle Genetics	91	Massachusetts Institute of Technology	53
ImmunoGen	56	ImmunoGen	66	Abbott Laboratories	50
Seattle Genetics	54	MedImmune	63	Scripps Research Institute	49
University of Utah	49	Novartis	59	Dana-Farber Cancer Institute	39
Sichuan University	48	Amgen	47	Fudan University	37
University of Washington	48	Daiichi Sankyo Company	43	Johns Hopkins University	36
Harvard Medical School	45	Genmab	38	Agency for Science, Technology and Research	34
Northeastern University	40	Bristol-Myers Squibb Company	36	Yale University	30
University of Texas	40	Biogen	34	Duke University	29
Memorial Sloan Kettering Cancer Center	39	Jiangsu Hengrui Med. / Shanghai Hengrui Pharm.	33	General Hospital Corporation	29
Zhejiang University	39	Medarex	32	Memorial Sloan Kettering Cancer Center	29
University of Michigan	38	Pfizer	32		
		Pierre Fabre Medicament	32		
		Innovent Biologics (Suzhou)	31		
		Seagen	31		
		AbbVie	29		
		Human Genome Sciences	29		
		Janssen Biotech	29		

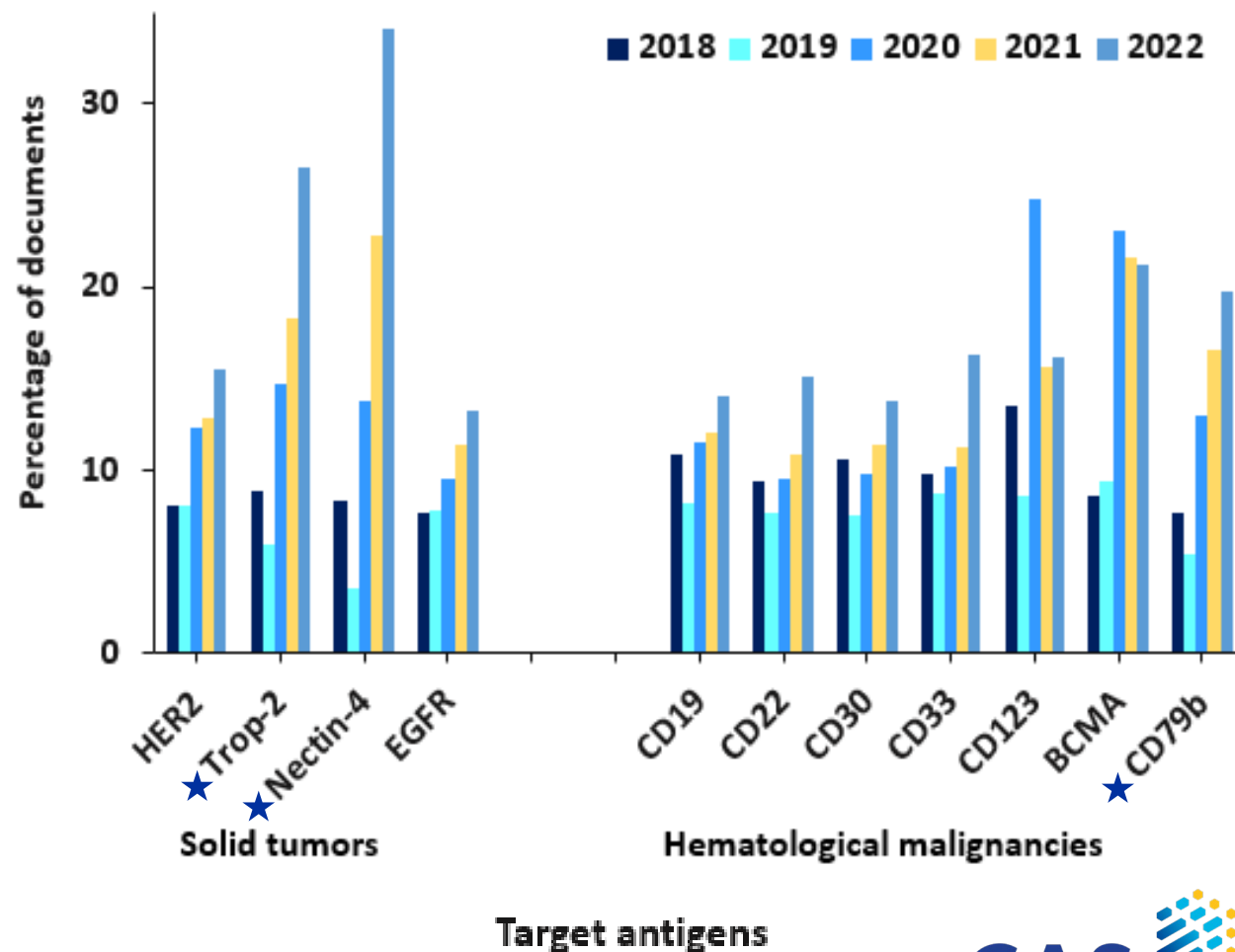
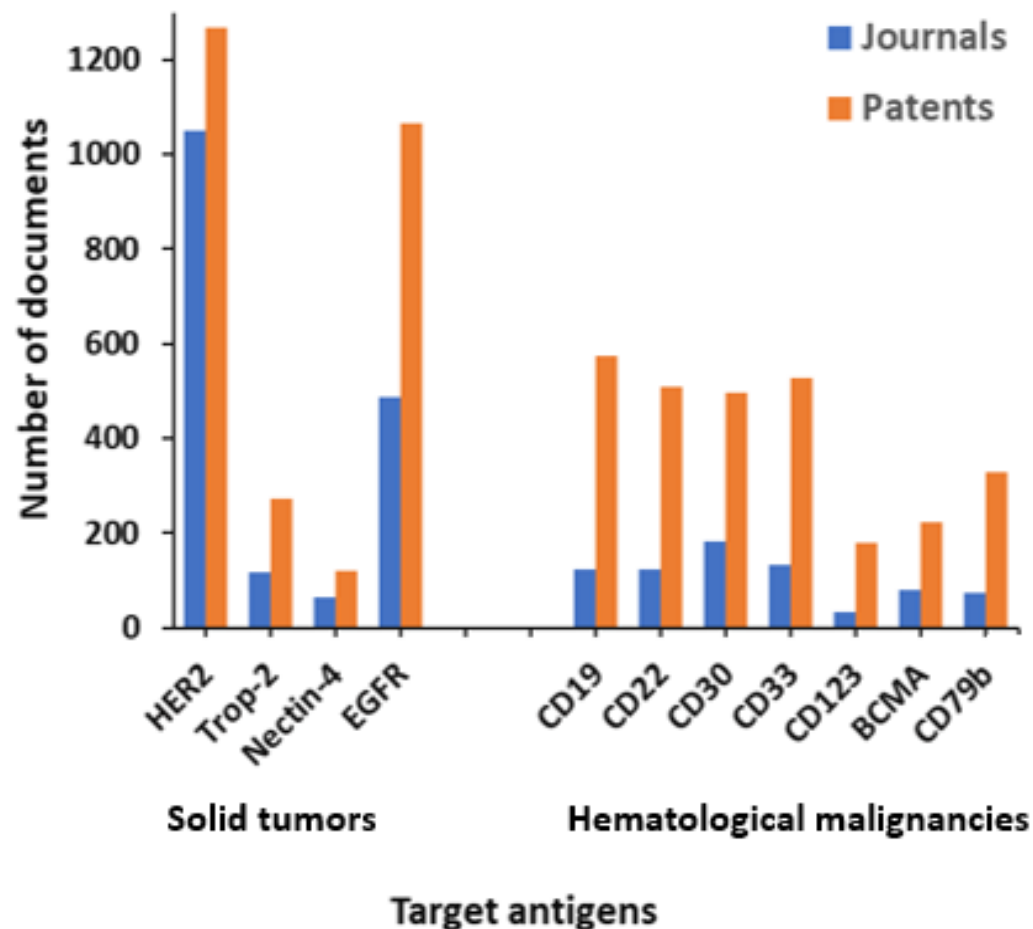
Diseases explored with ADCs

Cancers and non-cancerous diseases



Target antigens

HER2 and EGFR most widely explored for solid tumors



Correlation between cancer and ADC target antigens

Solid tumors

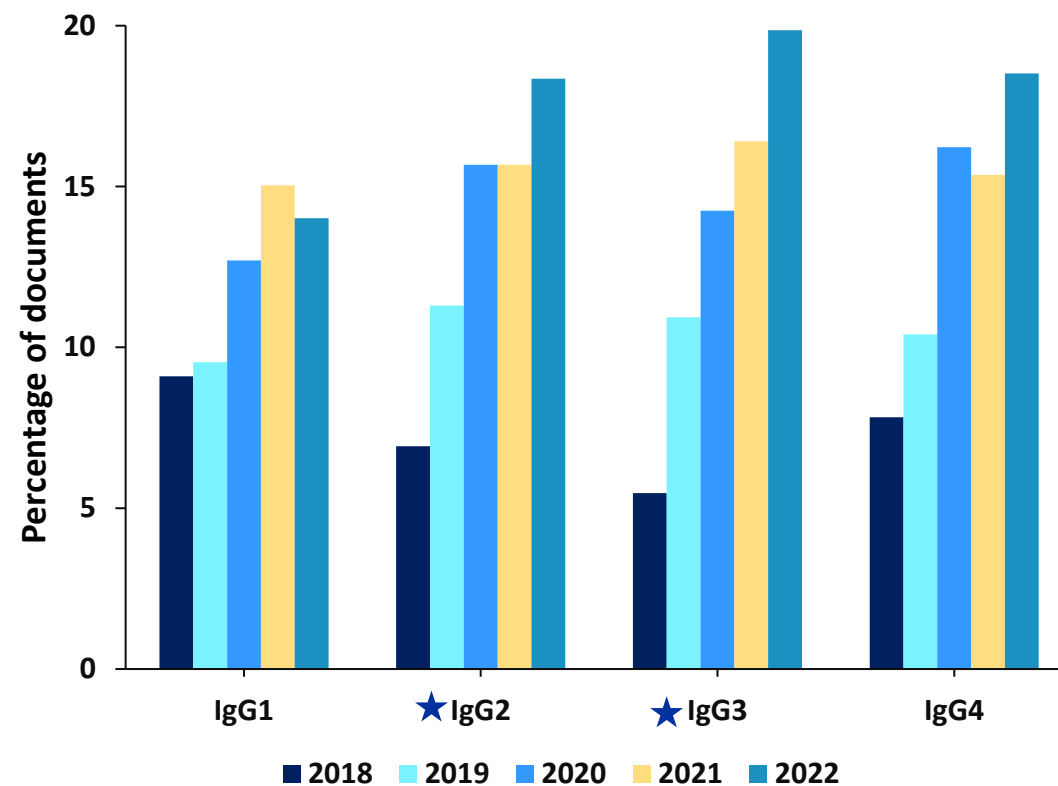
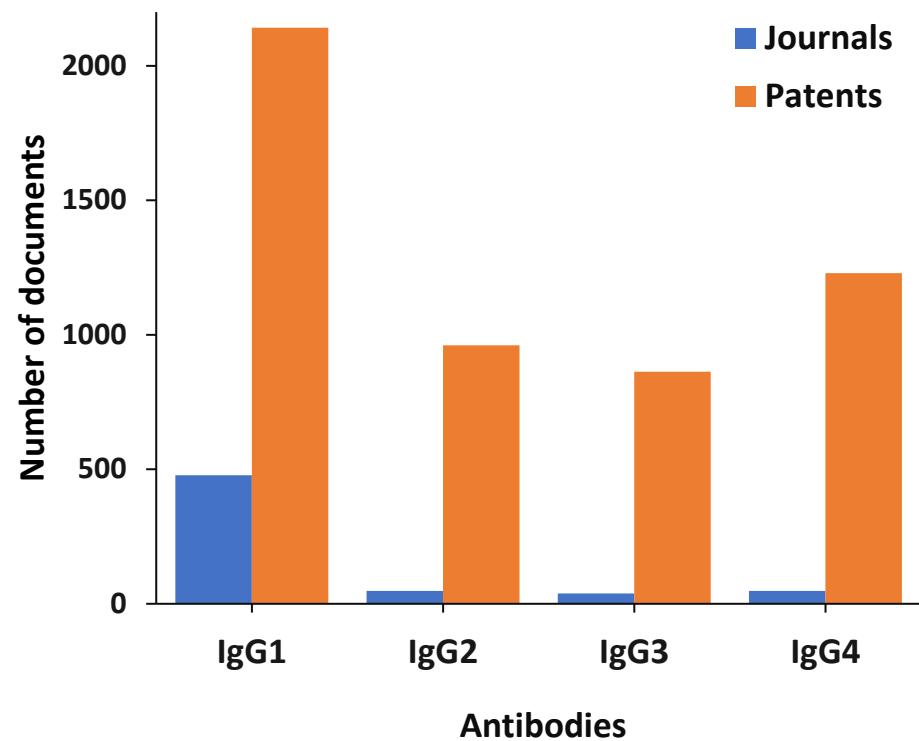
	HER2	Trop-2	Nectin-4	EGFR
breast cancer	67	9	2	22
ovarian cancer	45	13	6	37
prostate cancer	43	13	5	39
lung cancer	43	12	5	40
pancreatic cancer	38	20	7	35
cervical/uterine cancer	43	15	4	38
stomach cancer	45	13	5	37

Hematological malignancies

	CD19	CD22	CD30	CD33	CD123	BCMA	CD79b
lymphoma	21	21	22	15	5	7	10
leukemia	21	19	15	24	7	7	7
myeloma	18	16	16	16	6	22	7

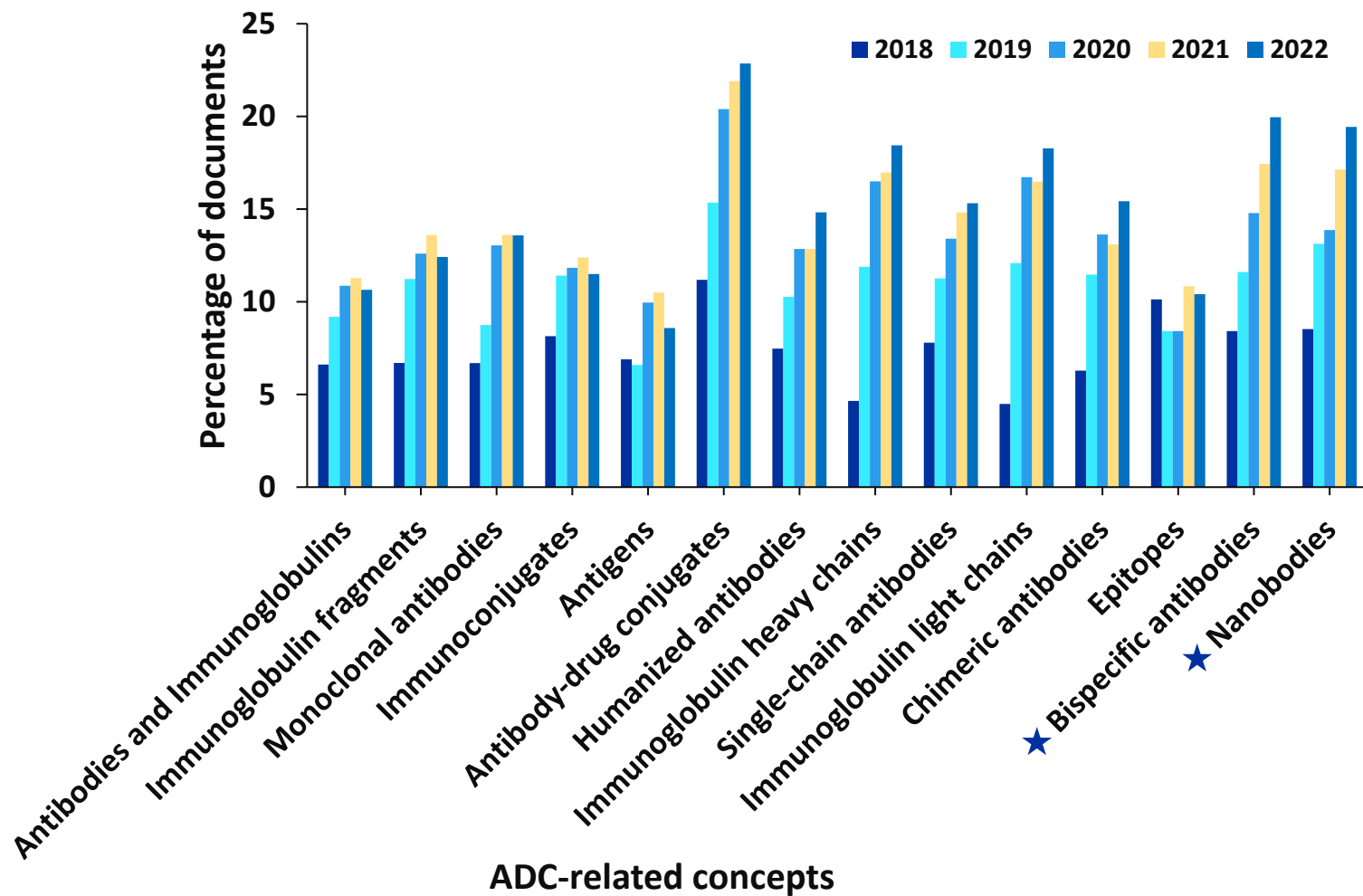
Antibodies

IgG1 and IgG4 are most frequently used in ADCs



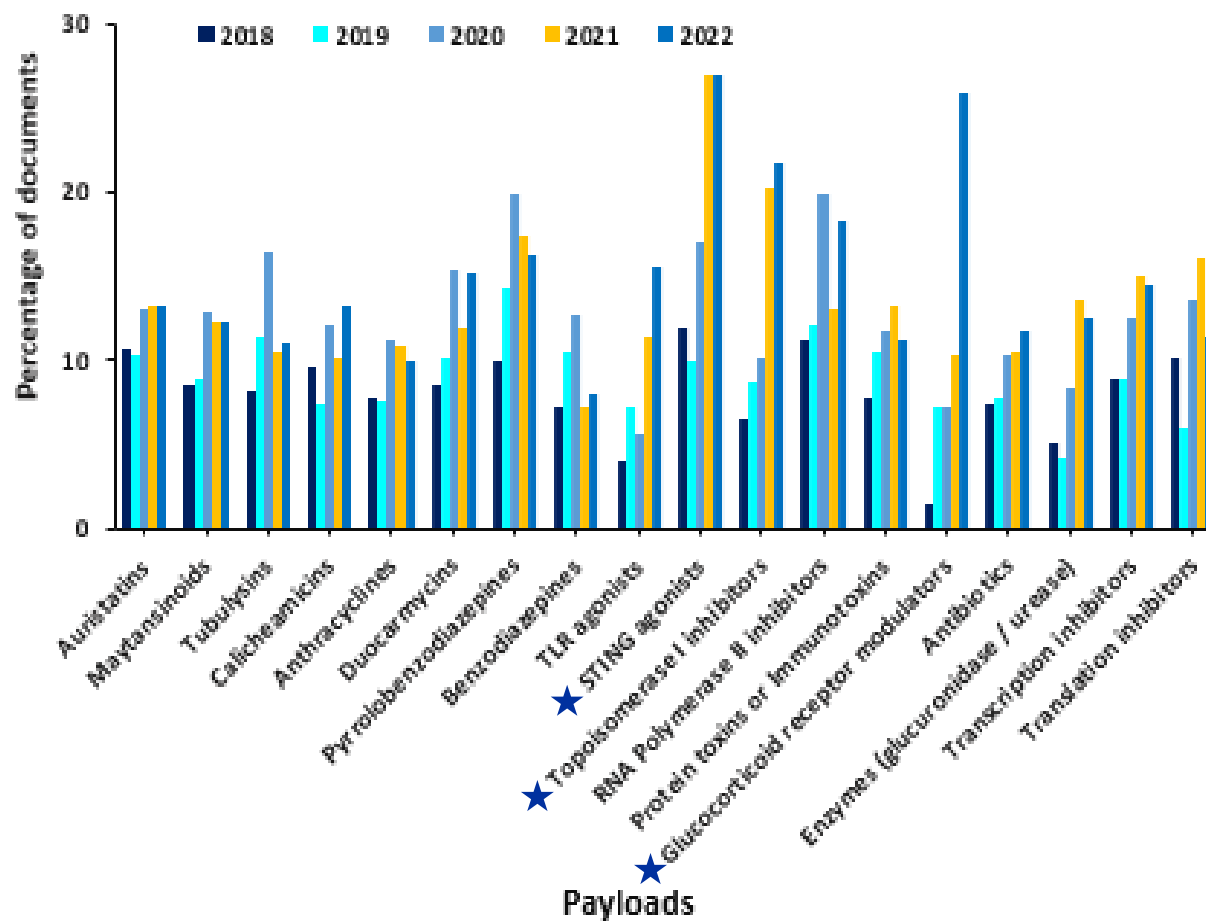
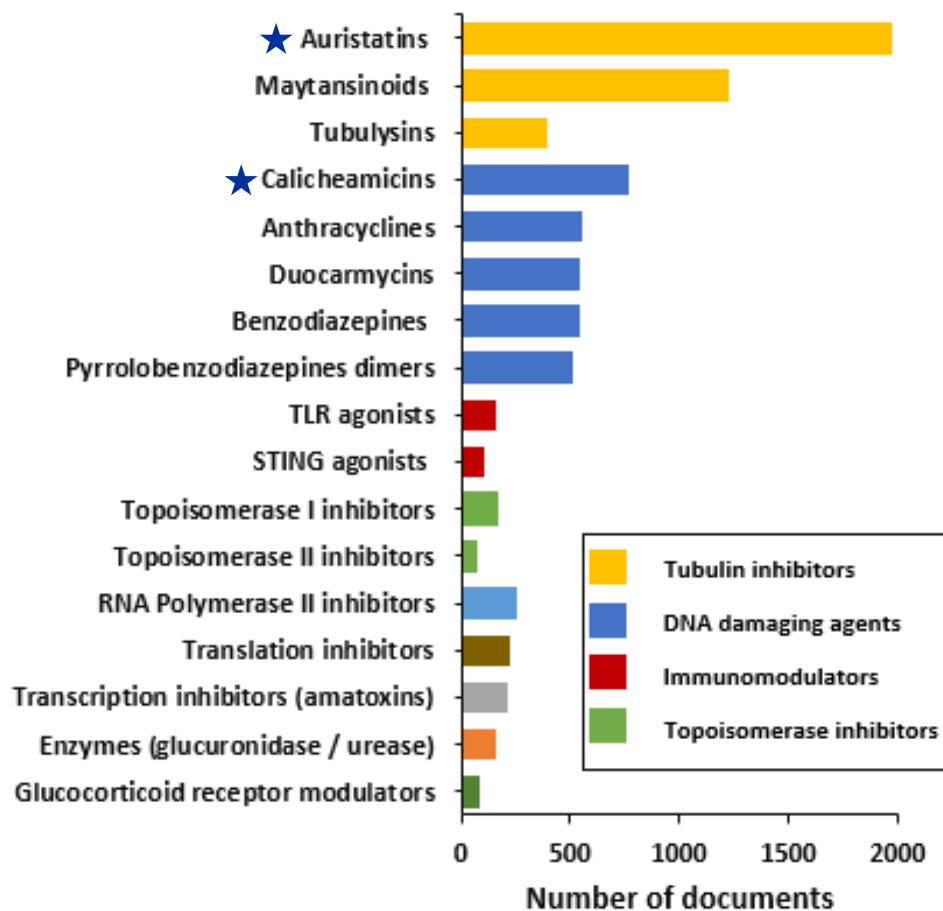
Growing areas of research

Bispecific antibodies and nanobodies



Common Payloads

Tubulin inhibitor Auristatins and DNA-damaging Calicheamicins



Correlation between cancer and ADC antibodies and payloads

Solid tumors	IgG1	IgG2	IgG3	IgG4
breast cancer	50	17	14	19
ovarian cancer	38	20	18	25
prostate cancer	37	20	18	25
lung cancer	39	19	17	24
pancreatic cancer	38	19	18	25
cervical/uterine cancer	38	20	18	24
stomach cancer	37	20	18	24

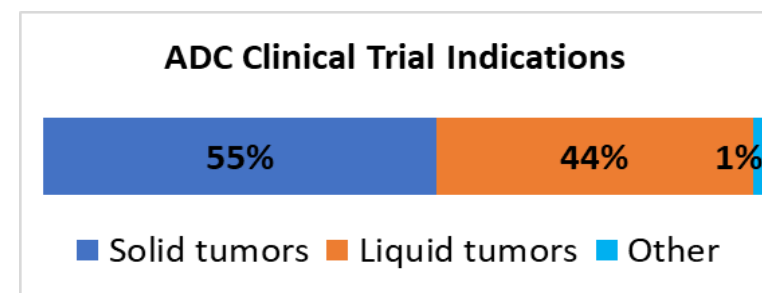
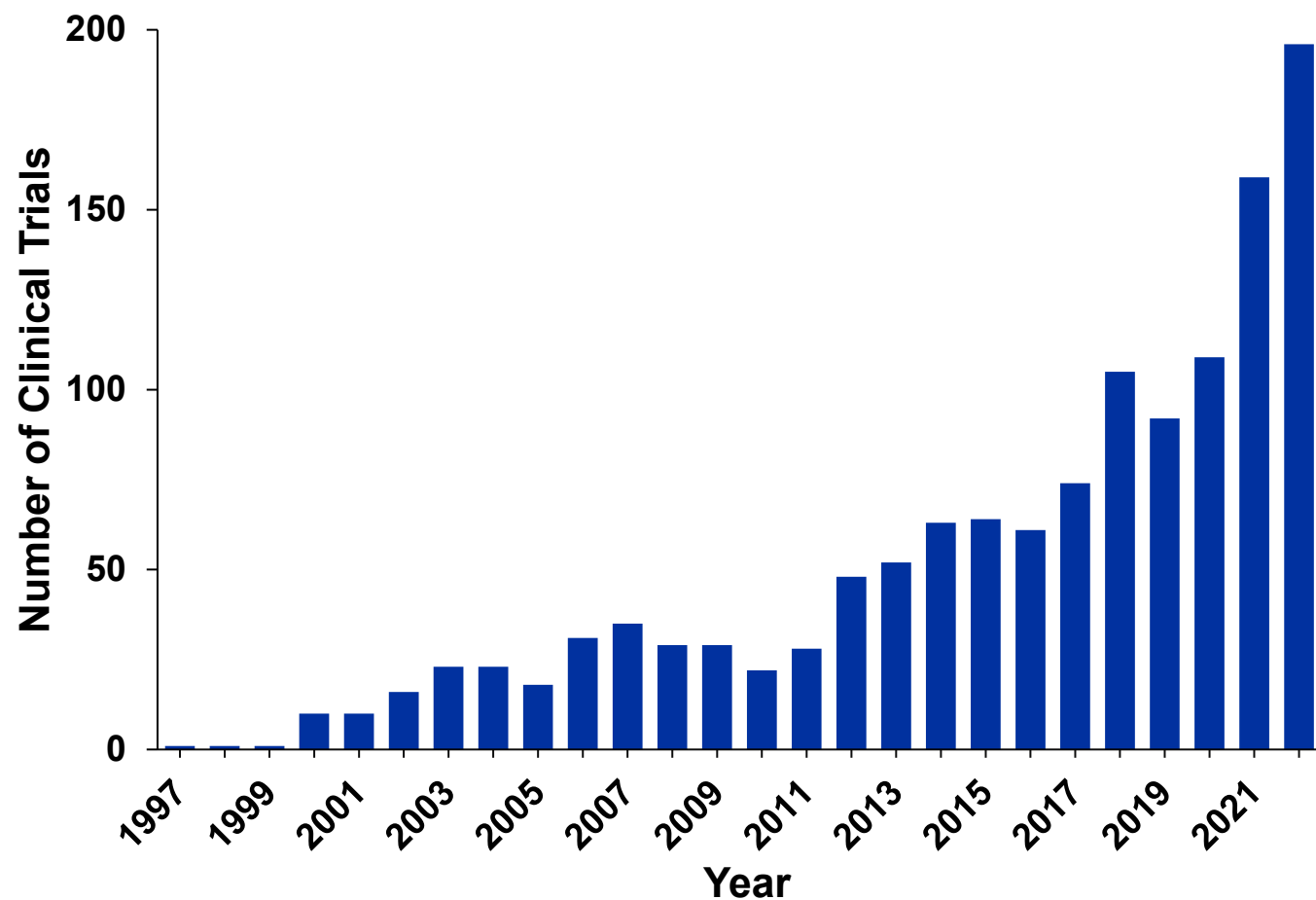
Hematological malignancies	IgG1	IgG2	IgG3	IgG4
lymphoma	40	18	17	25
leukemia	39	18	18	25
myeloma	38	18	18	26

Solid tumors	auristatins	maytansinoids	tubulysins	calicheamicins	duocarmycins	benzo-diazepines	topoisomerase inhibitors	RNA polymerase inhibitors
breast cancer	27	38	4	9	5	7	10	1
ovarian cancer	23	23	5	16	9	12	10	1
prostate cancer	22	22	5	16	9	13	12	1
lung cancer	25	24	5	15	8	12	11	1
pancreatic cancer	24	21	5	16	10	12	10	1
cervical / uterine cancer	22	23	4	17	10	11	12	1
stomach cancer	23	22	6	15	9	12	12	2

Hematological malignancies	auristatins	maytansinoids	tubulysins	calicheamicins	duocarmycins	benzo-diazepines	topoisomerase inhibitors	RNA polymerase inhibitors
lymphoma	26	21	5	16	9	14	9	1
leukemia	21	21	4	20	9	15	8	2
myeloma	22	21	5	17	9	12	11	2

Clinical trials

ADCs are accelerating in clinical development



Approved ADCs

15 with regulatory approval anywhere in the world

Drug	Trade name	CAS RN ®	Maker	Condition	Target	Approval Year	mAb	Linker	Payload	Payload Action	DAR	Conjugation	No. docs
Trastuzumab deruxtecan ^{63, 64}	Enhertu	1826843-81-5	AstraZeneca/ Daiichi Sankyo	unresectable or metastatic HER2-positive breast cancer	HER2	2019	humanized IgG1	maleimide-GGFG enzyme cleavable	DXd/ Camptothecin	TOPO1 Inhibitor	8	Cys	291
Sacituzumab govitecan ^{65, 66}	Trodely	1491917-83-9	Immuno-medics	metastatic triple-negative breast cancer	Trop-2	2020	humanized IgG1	CL2A acid cleavable	SN-38/ Camptothecin	TOPO1 Inhibitor	7.6	Cys	237
Loncastuximab tesirine-lpyl ^{69, 70}	Zynlonta	1879918-31-6	ADC Therapeutics	large B-cell lymphoma	CD19	2021	IgG1	enzyme cleavable	SG3199/ PBD dimer	DNA cleavage	2.3	Cys	66
Tisotumab vedotin-tftv ^{71, 72}	Tivdak	1418731-10-8	Seagen Inc	recurrent or metastatic cervical cancer	Tissue factor	2021	IgG1	enzyme cleavable	MMAE/ Auristatin	microtubule Inhibitor	4	Cys	55
Cetuximab Sarotalocan ^{21, 73, 74}	Akalux	2166339-33-7	Rakuten Medical	unresectable locally advanced, recurrent head & neck cancer	EGFR	2021	IgG1	N/A	IRDye700DX	photo-sensitizer	1.3–3.8	Lys	2
Disitamab Vedotin ^{75, 76}	Aidixi	2136633-23-1	RemeGen	HER2-overexpressing gastric cancer	HER2	2021	IgG1	enzyme cleavable	MMAE	microtubule Inhibitor	4	Cys	15
Mirvetuximab soravtansine ^{77, 78}	Elahere	1453084-37-1	ImmunoGen	platinum-resistant ovarian cancer	FR α	2022	IgG1	enzyme cleavable	DM4	microtubule inhibitor	3.4	Cys	87

Major perspectives on ADC development

Combination Therapies

- Combining ADCs with chemotherapies, radiation therapy, or other immunotherapies (checkpoint inhibitors)
- Overcome resistance mechanism and enhance therapeutic outcomes
- Recent FDA approval (April 2023) Padcev (Astellas Pharma) with Keytruda (Merck)

Companion Diagnostics

- Biomarker identification and patient stratification based on target expression levels or other predictive factors
- Help select the most appropriate patients for treatment and improve the clinical outcome of ADC treatment

Acknowledgement

CAS colleagues and teammates

- Janet Sasso
- Rumiana Tenchov
- Robert Bird
- Kavita Iyer
- Krittika Ralhan
- Qiongqiong Angela Zhou

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