Emerging Targets and Therapeutics in Immuno-Oncology Landscape: Insights from Natural Language Processing Analysis

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Abstract (~293 words)

Rapid and sustained growth in the field of immuno-oncology has resulted in expansion of available scientific literature. Gaining valuable insights and establishing deep and often hidden meaningful connections in such a large body of work is the need of the hour. In this report we summarize our findings from a novel Natural Language Programming (NLP)-based approach on a large dataset of >350K scientific publications in immuno-oncology research spanning across two decades (2000-2022) retrieved from the CAS Content Collection. Our analysis led to identification of >300 emerging concepts across major categories such as therapeutic targets, biomarkers, therapies, and types of cancer. We present a "Trend Landscape Map" of emerging concepts in immuno-oncology possessing layers of intricacies – at first glance providing information for the >300 identified concepts arranged hierarchically across 8 major categories and at a deeper level providing detailed quantitative metrics of growth over the last three years (2020-2022). While concepts such as immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs) and chimeric antigenic receptors (CARs) continue to be important in immuno-oncology, their growth over the last three years have been modest. On the other hand, concepts including protein targets such as TROP2, nectin-4, and gasdermins display rapid increase in scientific publications over 2020-2022 while their absolute number of publications remain low potentially indicative of early emergence. Finally, guided by our trend landscape analysis, we performed substance data analysis leveraging data from >3.2 million substances from the CAS Registry and identified potential higher commercial interest in protein/peptide sequences rather than small molecules in cancer immunotherapy as seen with respect to patent publications. It is our hope that our subject matter experts' knowledge-guided big data analysis approach based on the corpus of robustly CAS indexed data provides a comprehensive picture of immuno-oncology as it stands today with the trend landscape map serving as a valuable resource to researchers in this field.

Keywords: natural language processing, landscape analysis, immuno-oncology, trend map, emerging concepts, cancer

Introduction

Cancer has been declared as one of the leading causes of death by the World Health Organization (WHO).[1] The global economic burden of cancer is undeniable with projections estimating nearly $25 trillion in the year 2050.[2] In the United States alone ~600K deaths have been estimated in 2023.[3] In this bleak landscape, immuno-oncology – a field at the forefront of cancer research and treatment, has emerged as a beacon of hope in the fight against various types of cancers. Harnessing the body's immune system to recognize, target, and eliminate tumor cells, immuno-oncology's extraordinary promise and rapid growth have captured the attention of researchers and pharmaceutical industries worldwide. This burgeoning potential and heightened interest are vividly reflected in the growing number of scientific publications (Fig. 1a), especially in the last four years, and the escalating number of drugs under evaluation in clinical trials since 2015 (Fig. 1b) accounting for ~5,500 clinical trials currently ongoing across various clinical phases.

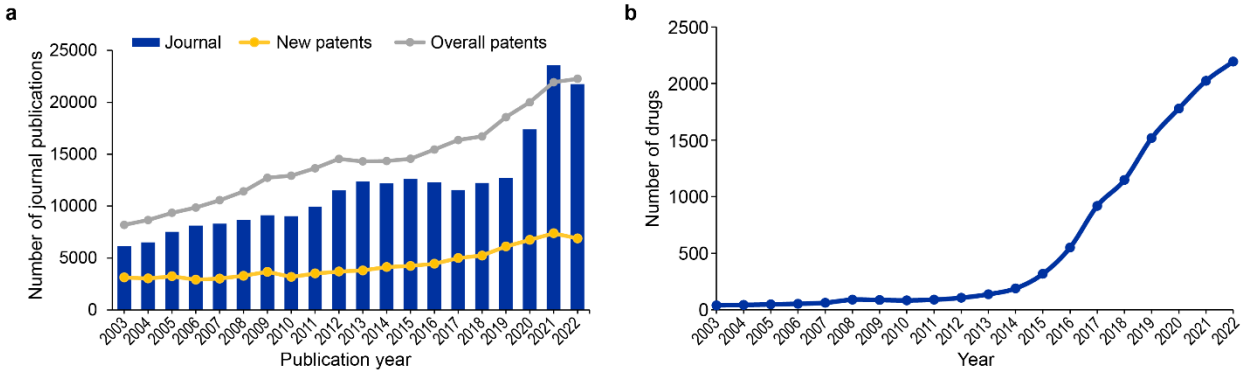

Fig. 1 | a, Overall growth in publications (journals and patents) pertaining to immuno-oncology from the CAS Content Collection over the last two decades (2003-2022). The blue bars represent journal publications while the yellow line represents new patent publications, and the grey line represents the total number of patent publications reflective of overall patent activity. **b**, Growth in the number of drugs in the field of immuno-oncology in the preclinical stage over the last two decades (2003-2022); data retrieved from Pharmaprojects.

Amongst the better-known cancer immunotherapies are immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs). The discovery and development of ICIs has been revolutionary for cancer therapy and has led to a paradigm shift.[4] Therapeutic success of US Food and Drug Administration (FDA) approved ICIs Keytruda[5] (pembrolizumab; Merck & Co.) and Opdivo[6] (nivolumab; Bristol Myers Squibb) in treating melanoma[7,8] and non-small cell lung cancer (NSCLC)[9] among other types of cancer has been encouraging. Besides ICIs, US FDA approved ADCs such as Kadcyla[10] (ado-trastuzumab emtansine; Genentech Inc.), Besponsa[11] (inotuzumab ozogamicin; Pfizer Inc.) and Elahere[12] (mirvetuximab soravtansine; ImmunoGen Inc.) have also shown tremendous success in the treatment of metastatic breast cancer,[13] acute lymphoblastic leukemia[14] and ovarian cancer,[15] respectively. The remarkable success of ADCs[16] has meant that the scope of ADCs is expanding beyond the boundaries of cancer.

Out of the 46 novel drugs that have gained US FDA approval in 2023 alone,[17] over 15% are associated with cancer immunotherapy including the monoclonal antibodies (Loqtorz/toripalimab-tpzi[18] and Zynyz/retifanlimab-dlwr[19]) against the immune checkpoint

molecule programmed cell death 1 receptor (PD-1), and bispecific T-cell engagers directed towards CD20 (Columvi/glofitamab[20]) and B-cell maturation antigen (BCMA) (Elrexfio/elranatamab-bcmm[21]). The therapeutic and commercial success of ICIs and ADCs and the continued regulatory approvals of new cancer immunotherapeutic drugs has translated to impetus for pharmaceutical companies to continue investing in this field with a sustained interest in developing newer/novel immunotherapeutic drugs. This is exemplified by the nearly $16 billion in investments for cancer immunotherapy in 2022-2023 (Pitchbook[22]).

The pursuit of advancements in immuno-oncology by academic and commercial organizations has led to proliferative, sustained, and rampant expansion of journal and patent publications. In this report, leveraging the extensive CAS Content Collection™, we delved deep into this fast-growing corpus of scientific publications aiming to identify emerging trends that will be invaluable to researchers in this vibrant community. We utilized a novel natural language processing (NLP)-based algorithm[23] in combination with extensive curation by subject matter experts resulting in quantitative identification of >300 emergent topics across eight main areas of interest. Moreover, our analysis allowed us to capture ideas that appear to be in the very early/nascent stages of emergence. We have designed a trend landscape map to illustrate the spread of emerging ideas in immuno-oncology across a wide range of topics with an emphasis on their growth over the last 3 years.

Trend Landscape Map: A bird's eye view of emerging concepts in immuno-oncology

Our dataset comprises ~350K publications extracted from the CAS Content Collection, the largest human-compiled multi-disciplinary database of published documents and substances, employing a comprehensive search query developed by subject matter experts. The extracted data consisting of a wide range of information, including extensive bibliographic information, CAS indexed concepts and substances, was subjected to NLP[23] to identify frequently used phrases (for detailed description of methods see Supplementary Information and Supplementary Fig. 1). Subsequently, these phrases underwent exhaustive manual scrutiny by subject matter experts, forming the basis for calculating the relative rates of publication growth over the period 2020-2022.

The identified emerging concepts were categorized into eight major domains – targets, therapies, interleukins, RNA-related, side effects, mechanism-based, biomarkers, and types of cancer. To visually represent these trending and emerging concepts, we constructed a trend landscape map (Fig. 2) featuring a hierarchical arrangement of emerging concepts within pertinent groups and incorporated data from journal and patent publications (Fig. 2). Most identified concepts ended up being clustered in the following four categories: types of i) targets, ii) therapies, iii) cancers and iv) biomarkers. The trend landscape map has been designed to provide at a glance: the average fold increase in publications over 2020-2022 and the number of publications over 2020-2022 using a color scale and symbols, respectively. Broadly speaking, the identified concepts grew at a modest (1.1 to 1.5X), fast (1.6 to 2X) or very fast (2 to >3X) pace. In addition, for the reader's ease, we have highlighted the relative growth rates of the fastest growing concepts in each of the 4 most prolific categories: types of targets, biomarkers, cancers, and therapies (see Fig. 3). Both, average fold increase as well as relative growth rate are metrics indicating scientific interest albeit expressed differently with the latter being normalized with respect to number of publications.

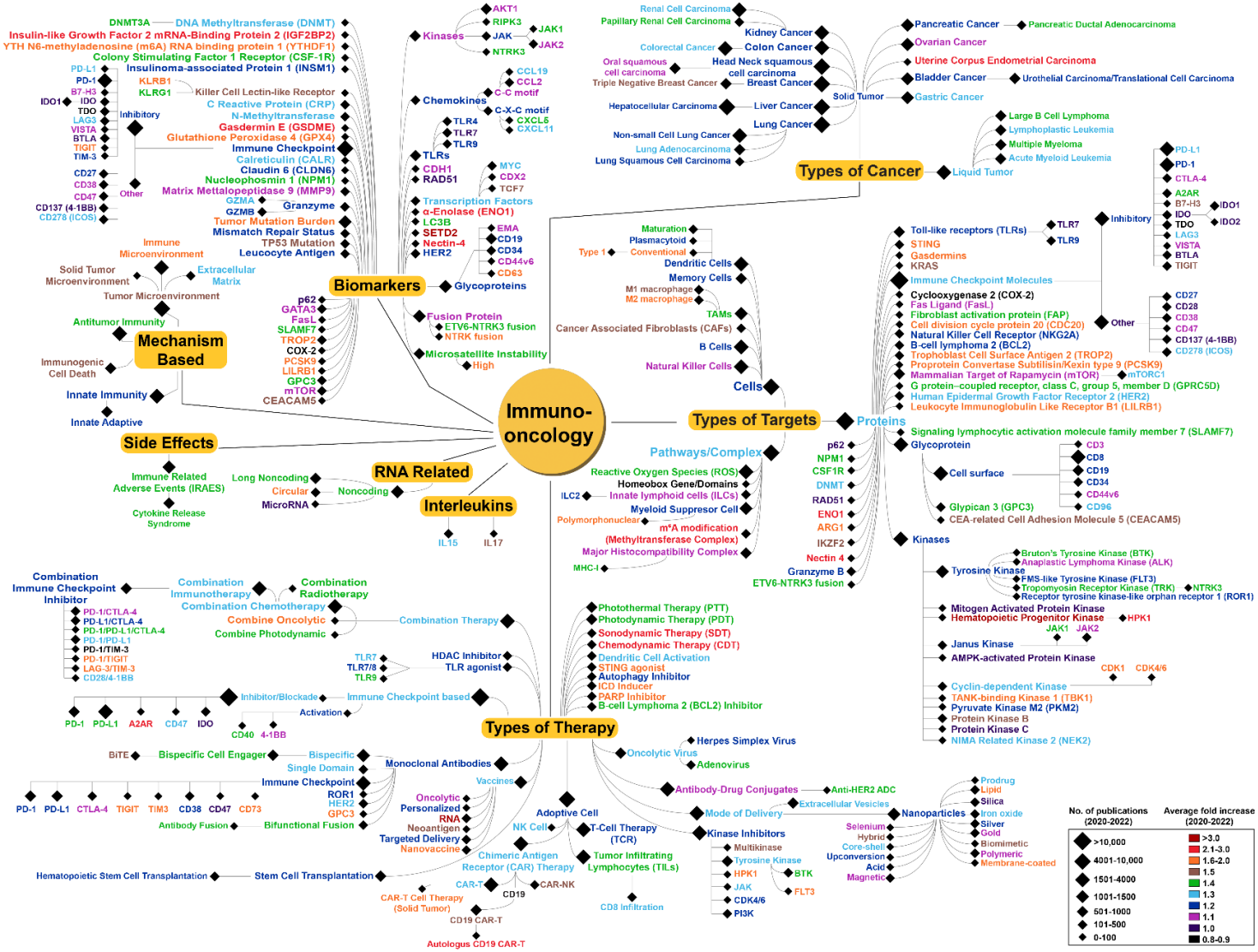

Fig. 2 | Detailed "Trend Landscape Map" of emerging concepts/ideas in immuno-oncology curated from NLP data analysis on >350,000 publications from the CAS Content Collection. The size of the symbol (◆) corresponds to the number of publications for the period 2020-2023 while the color of the text indicates the average fold increase in publications for the period 2020-2023 – an indicator of growth. For detailed description of average fold increase please see Methods in Supplementary Information.

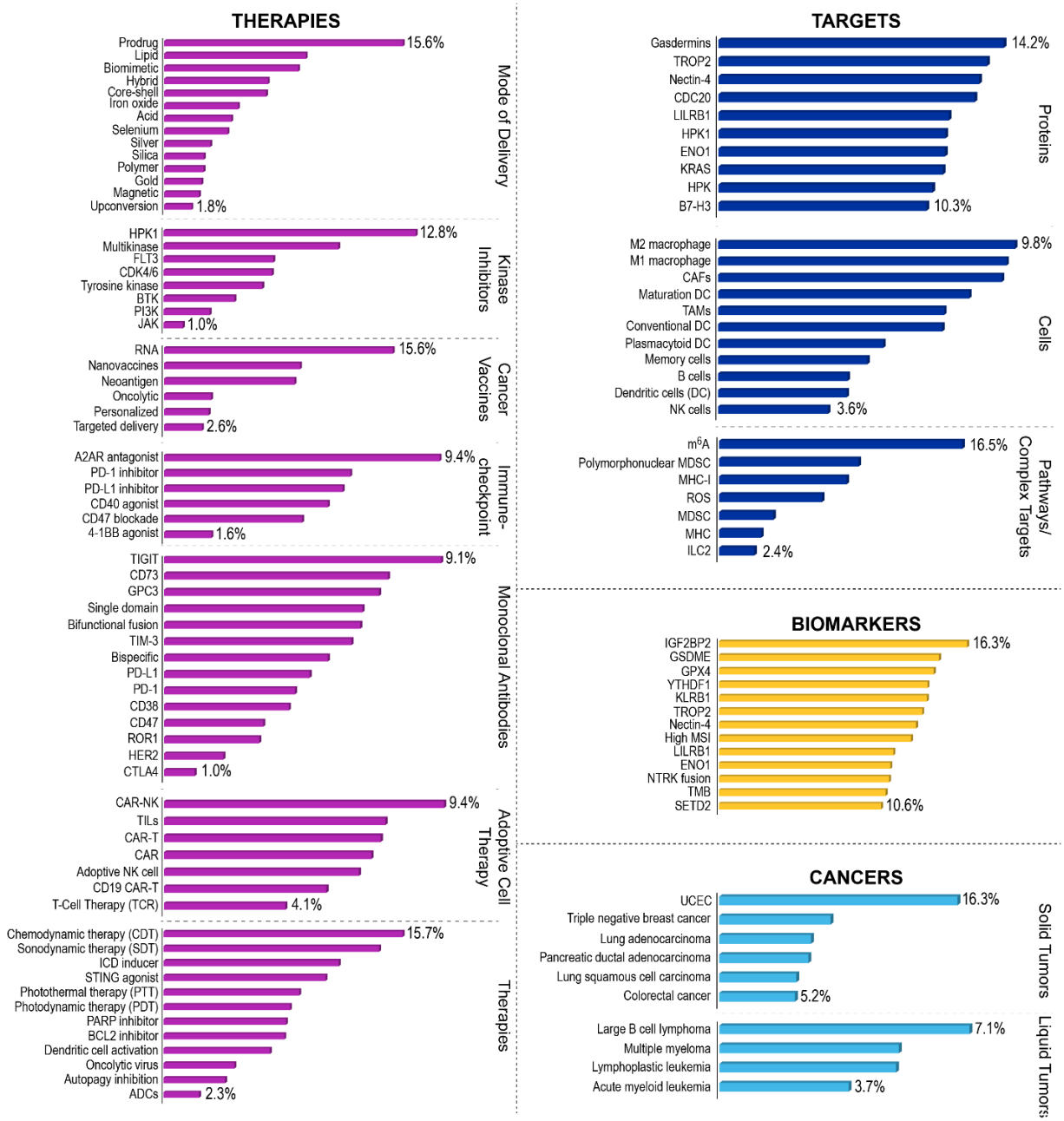

Fig. 3 | Fastest growing concepts in a few selected major immuno-oncology-related categories from NLP data analysis on >350,000 publications from the CAS Content Collection. Data includes both journal and patent publications and expressed as relative growth rates (which are average publication rates normalized with respect to number of documents) for the period 2020-2022. For more detail, please see Methods in Supplementary Information.

Out of the ~100 identified emerging targets, publications for protein targets such as gasdermins,[24] STING,[25] cell division cycle protein 20 (CDC20),[26] trophoblast cell-surface antigen 2 (TROP2),[27] proprotein convertase subtilisin/kexin type 9 (PCSK9),[28] leucocyte immunoglobulin like receptor B1 (LILRB1),[29] and cyclin dependent kinases (CDK1[30] and CDK4/6[31]) have doubled while those for nectin-4,[30] α-enolase 1 (ENO1),[31] and hematopoietic progenitor kinase[32] have nearly tripled over the last three years (2020-2022). Concepts/Areas of interest where the relative

growth rates of publications are high despite low absolute number of publications might indicate burgeoning and unmet interest (Fig. 4, Supplementary Figs. 2-4) – potential examples include gasdermins, TROP2, and nectin-4, all of which are amongst the fastest growing concepts with relative growth rates averaging >10% over the last three years (Figs. 2 and 3). In contrast, for concepts such as immune checkpoint molecules, kinases, and glycoproteins, the gap between pace of growth and absolute number of publications is not as stark, indicating that these concepts might be at the later stages of emergence (Fig. 4a). For about half of the identified emerging targets, the number of publications increased by 1.1-1.5X (moderate pace); a few representative ones are human epidermal growth factor receptor 2 (HER2),[33] toll-like receptors (TLRs),[34] and mammalian target of rapamycin (mTOR)[35] (Figs. 2 and 4a). A few targets appear to grow at a slow pace such as cyclooxygenase-2 (COX-2)[36] (Fig. 2).

Delving deeper into inhibitory immune checkpoint molecules, publications for T cell immunoreceptor with Ig and ITIM domains (TIGIT)[37] and B7-H3[38] grew on an average 1.5X over the last three years (Fig. 2) and might be emerging rapidly as compared to the rest of the checkpoint molecules (Fig. 4b). PD-1 and programmed cell death ligand 1 (PD-L1)[39] appear to be growing at a modest pace while others such as indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO),[40] enzymes vital for tryptophan degradation, appear to be growing slowly (Fig. 2). Hematopoietic progenitor kinase (HPK) and TANK-binding kinase 1 (TBK1)[41] among other kinases are emerging as the fast-growing concepts with publications appearing to have tripled or nearly tripled over the past three years (Figs. 2 and 4b). Other members of the kinase family such as janus kinase (JAK)[42] and pyruvate kinase M2 (PKM2)[43] are growing at a modest pace (Figs. 2 and 4b).

In terms of types of therapies, sonodynamic[44] and chemodynamic[45] therapies appear to be emerging at a rapid rate along with RNA based vaccines with publications tripling over the last three years (Fig. 2). Concepts such as chimeric antigen receptor T cell (CAR-T) therapy,[46] nanovaccines,[47] kinase inhibitors including HPK1[48] and FLT3 inhibitors,[49] among others are also growing at a fairly rapid rate (Fig. 2). Examples of therapies growing at a modest pace include anti-HER2 ADCs,[50] dendritic cell activators,[51] HDAC inhibitors,[52] and PI3K inhibitors[53] (Fig. 2).

Overall, targets and biomarkers tend to have a fair degree of overlap, and this is perhaps unsurprising since many biomarkers in cancer end up becoming targets for therapy. This could also be a result of the program picking up phrases outside of a given context (i.e., biomarker vs. target), though manual curation of data by subject matter experts have ensured where possible that concepts picked out are pertinent. Among biomarkers, nectin-4,[54] SET domain containing 2 (SETD2),[55] ENO1,[56] TROP2,[57] tumor mutation burden (TMB),[58] PCSK9,[59] and LILRB1[60] appear to be growing at a fast pace while p62,[61] COX-2[62] and TDO[63] show unremarkable/negligible growth (Fig. 2)

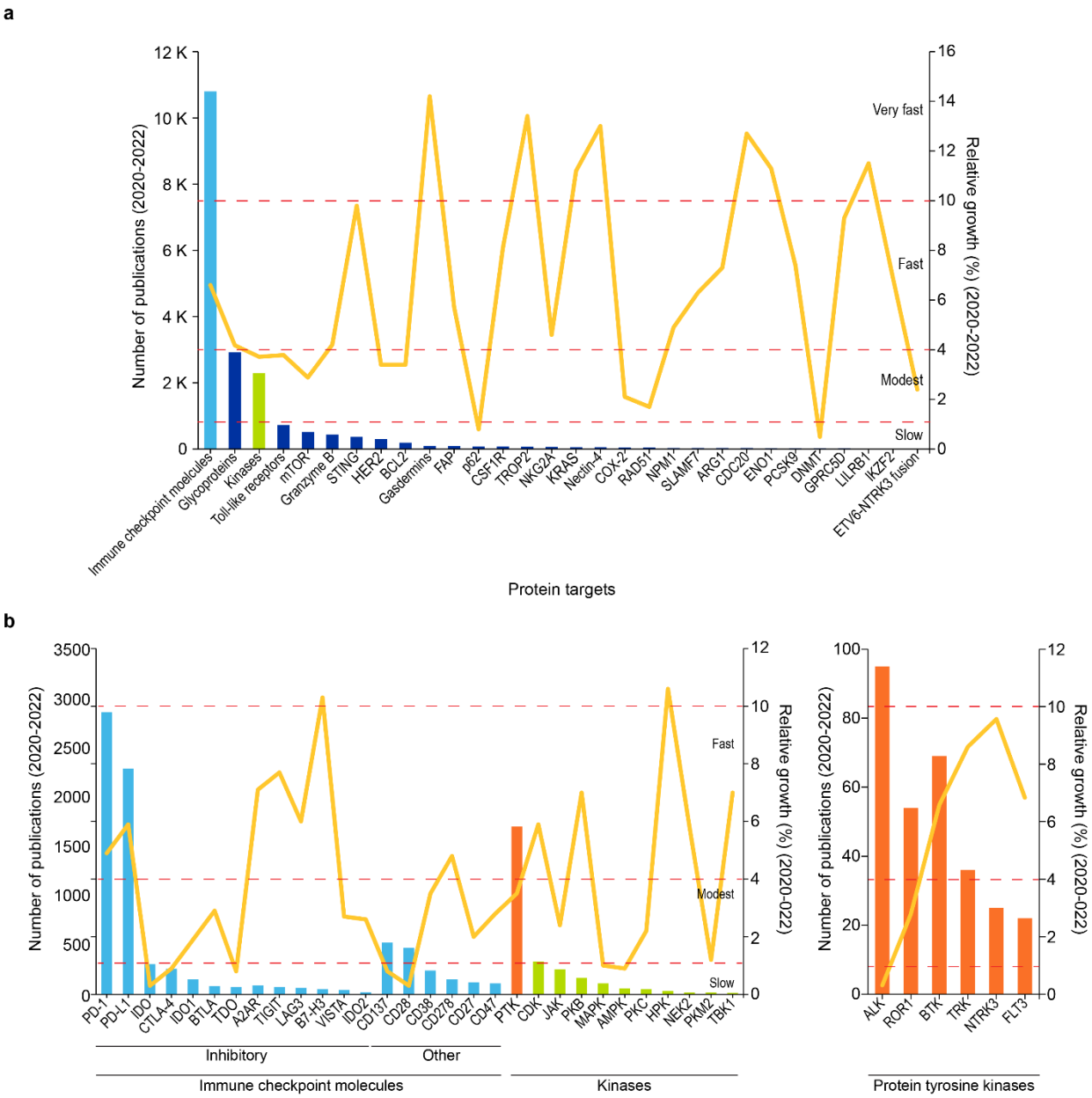

Fig. 4 | Comparison between relative growth rates (shown as yellow line) and number of publications (shown as colored bars) of **a**, protein targets and **b**, individual immune checkpoint molecules and kinase protein targets. Blue and green colored bars in panel a representing immune-checkpoint molecules and kinases, respectively, have been further broken down in panel b. Orange colored bar in panel b represents protein tyrosine kinases whose individual members are shown in the bottom right panel. Data from CAS Content Collection over 2020-2022. Targets can be divided into 4 categories of growth – very fast (>10%), fast (4-10%), modest (1-4%) and slow (<1%).

In addition to the trend landscape map, we also determined the year at which a particular concept starts to emerge and crafted timelines for the emergence of targets, therapies, and biomarkers in immuno-oncology (Fig. 5 and Supplementary Figs. 5 and 6). From the timeline of emerging targets in immuno-oncology (Fig. 5), it appears that while a majority of immune checkpoint molecules emerged in 2000s, others such as LAG3,[64] A2AR,[65] TIGIT,[66] and inducible

co-stimulators (ICOS, also known as CD278)[67] emerged much more recently, between 2011 and 2015. Protein targets such as nectin-4, TROP2, and gasdermins are among the ones that have emerged most recently, in 2017 (Fig. 3). Similar timelines for emerging biomarkers and therapies have also been generated (Supplementary Figs. 5 and 6).

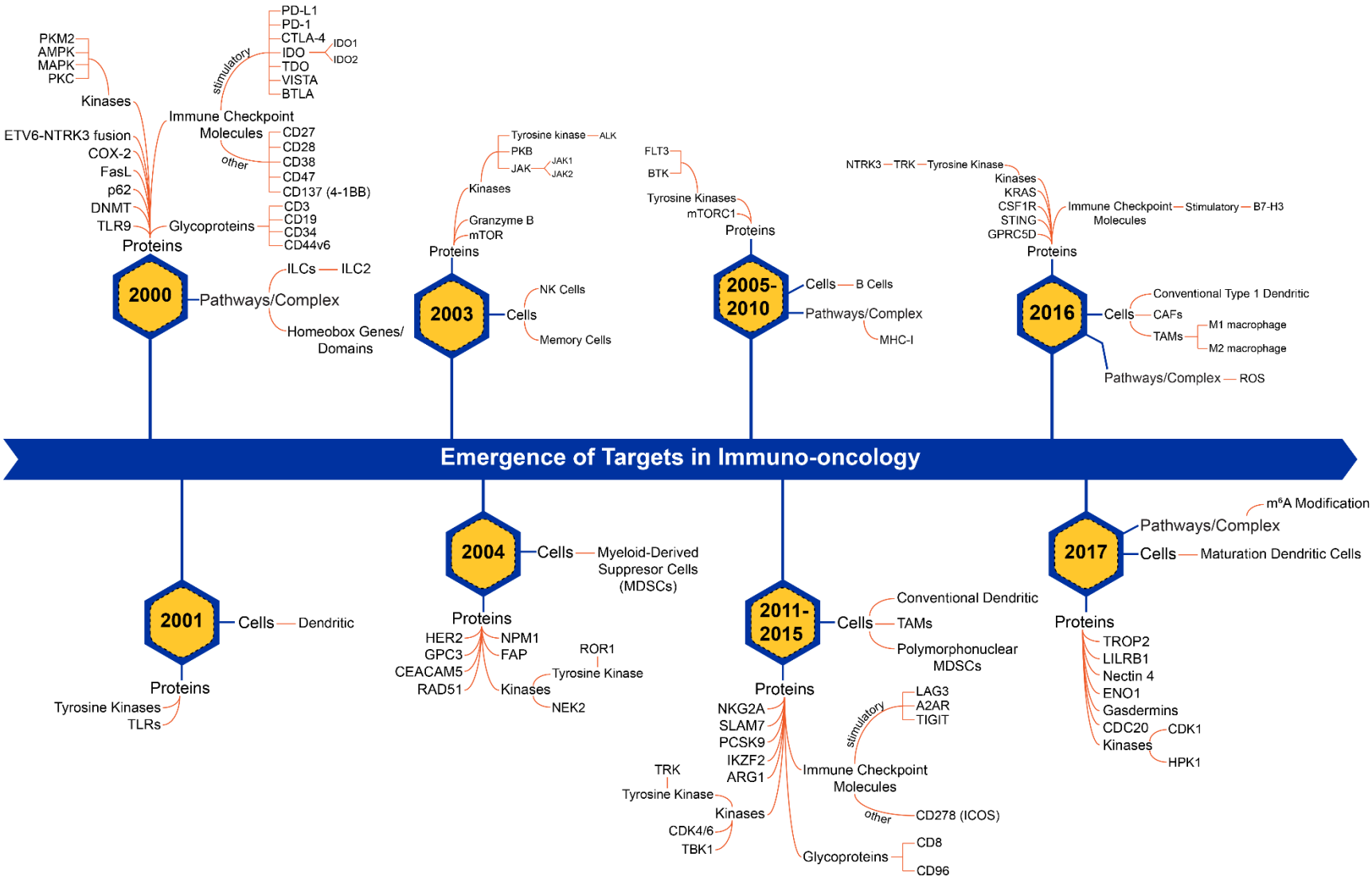

Fig. 5 | Estimated timeline of emerging therapeutic targets in the field of immuno-oncology based on NLP analysis of >350K publications from the CAS Content Collection for the period 2000-2022.

In depth view of the field of immuno-oncology: Publication and substances trends

We then delved deeper into trends in immuno-oncology covering journal and patent publications, their growth rates as well as co-occurrences between key areas of research.

In patent publications among commercial or non-commercial entities, the Unites States (USA) and China (CHN) dominate together accounting for nearly 60% and 54% of commercial and non-commercial patent publications, respectively (Fig. 6a). Other key players include: Germany (DEU), Japan (JPN), Switzerland (CHE), France (FRA), Republic of Korea (KOR), United Kingdom (GBR) – though the exact order of prominence varies for commercial vs non-commercial enterprises (Fig. 6a). Among commercial patent assignee entities, Bayer Healthcare and Genentech are leaders in terms of the number of patent publications, followed by Novartis, Bristol-Myers Squibb, Roche, and Merck (Fig. 6a). Patents held by these commercial organizations appear to be related to monoclonal antibodies, T cells, vaccines, ADCs, CARs, and ICIs among others.

Like patents, our data show similar trends for journal publications on country-wise distributions with China and the United States, together accounting for 65% of journal publications. The top three leaders in journal publications among the eight leading countries are highlighted in Fig. 6b. Within China, Huazhong University, Fudan University, and Sichuan University lead. Meanwhile in the United States, the University of Texas, Harvard Medical School, and the University of California are the leaders (Fig. 6b).

To gain insights into how different types of therapies have been investigated over the years, we analyzed the trends of selected emerging concepts that have shown commercial success in cancer immunotherapy, such as immune checkpoint-based therapies, CAR, ADCs, etc. The results indicate an upward trend for all the selected concepts with a steady growth in number of journal and patent publications over the past two decades (Fig. 7). Of special note are immune checkpoint-based therapies growing sharply after 2015 and nearly doubling between 2020-2022 (Figs. 7a and 7b). Since immune checkpoint-based therapy has been rising faster than others, we looked at the growth trajectory of individual checkpoint proteins. Within immune checkpoint molecules, PD-L1 and PD-1 show the greatest number of journal and patent publications with PD-L1 having nearly twice as many journal publications as all the other immune checkpoint molecules put together in 2022 (Fig. 7c). While PD-1 and PD-L1 dominate in terms of absolute number of publications, when looked at from the lens of relative growth, other immune checkpoint molecules such as B7H3, LAG3, and VISTA appear to be keeping pace with PD-1 and PD-L1 (Supplementary Fig. 7).

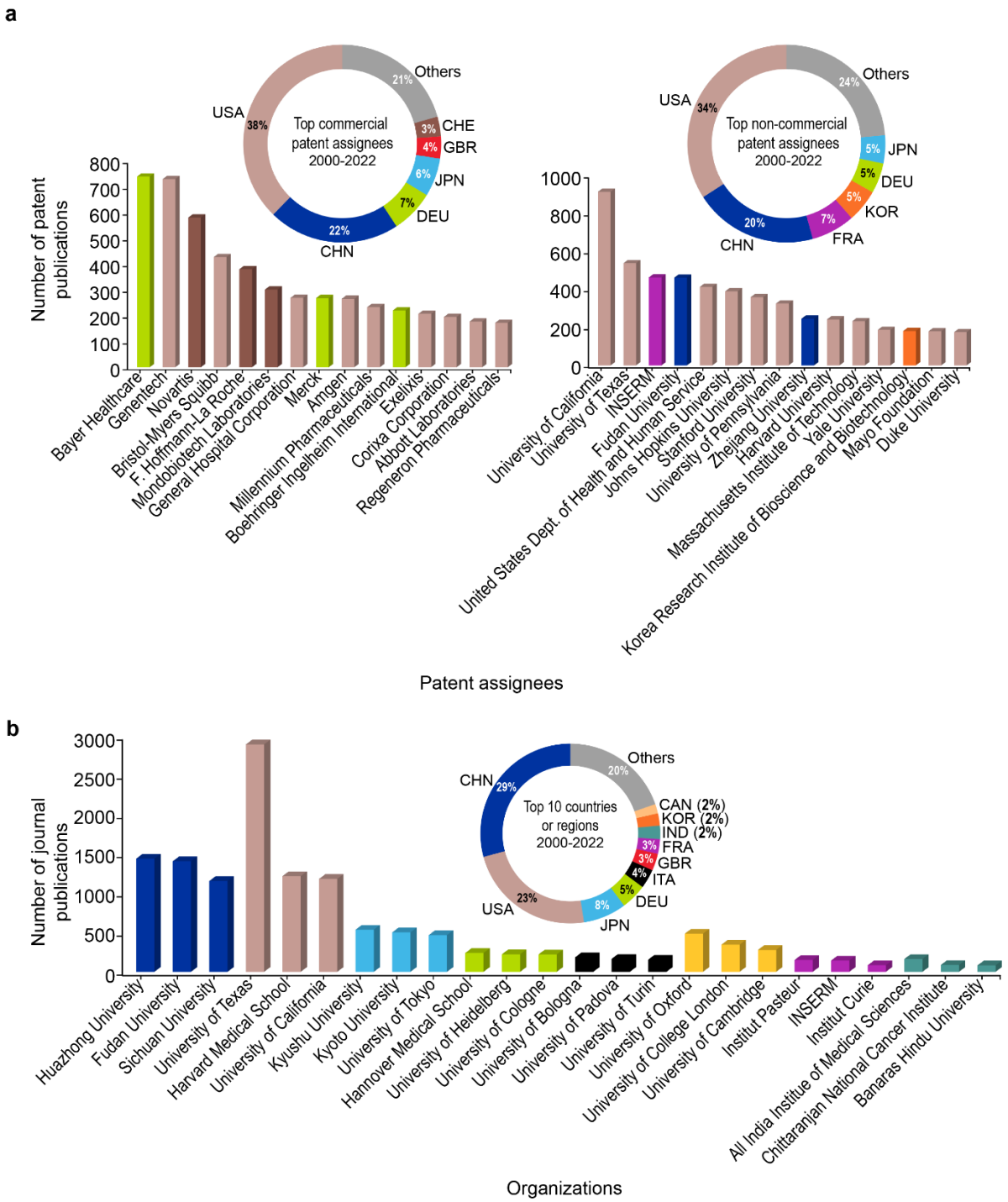

Fig. 6 | **a**, Donut charts indicate distribution of the top 6 countries or regions in terms of patent publications for commercial and non-commercial organizations while bar graphs show breakdown of top 15 patent assignee organizations. **b**, Donut chart indicates top 10 countries or regions in terms of journal publications for non-commercial organizations while the bar graph shows top 3 non-commercial organizations for each of the eight most prolific countries or regions in terms of journal publications. Bar graphs have been colored to match country-specific colors in the donut charts. Data includes publications from the CAS Content Collection for the period 2000-2022.

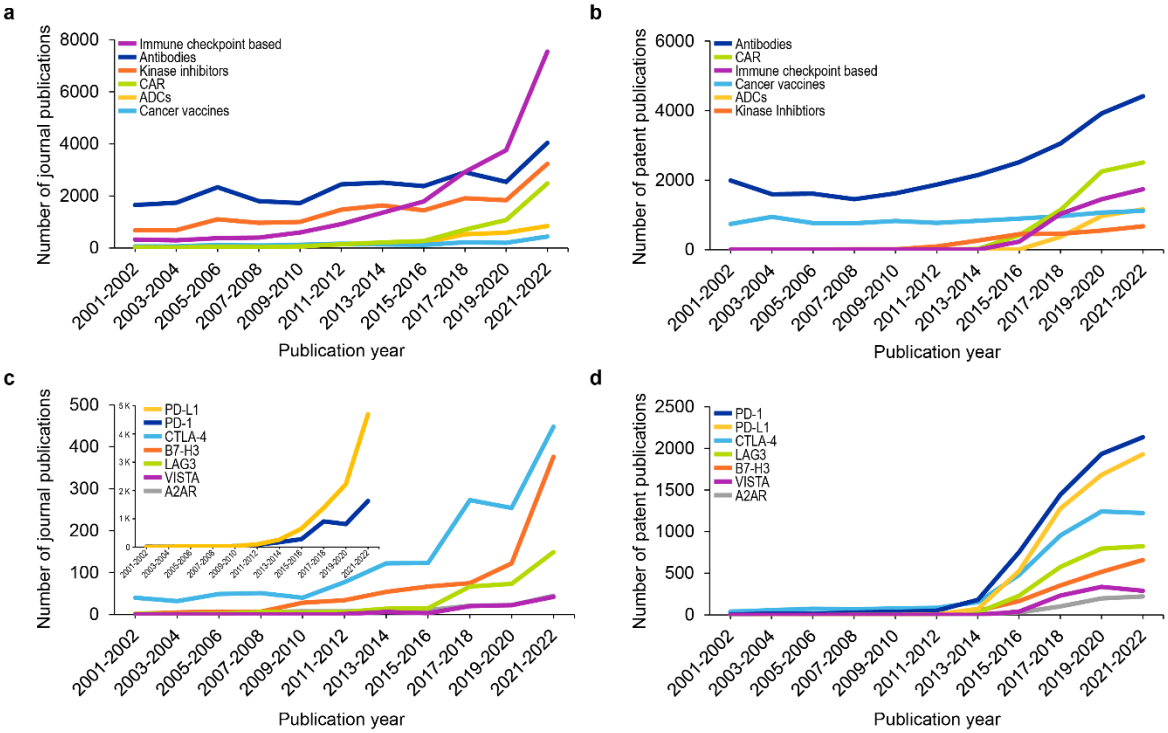

Fig. 7 | Growth of selected scientific concepts over the last two decades in terms of number of publications. **a**, Journal and **b**, patent publication trends of selected therapy-related concepts and **c**, journal and **d**, patent publication trends of selected individual immune checkpoint molecules. Data includes publications from the CAS Content Collection for the period 2001-2022.

To illustrate the connection between emerging therapies and different types of cancer, we determined instances of co-occurrences among related concepts as shown in sankey graphs (Fig. 8). Among the different types of emerging therapies - kinase inhibitors, immune checkpoint-based therapies, cancer vaccines, ADCs, CAR, and TILs appear to co-occur to a larger extent with emerging solid tumors in journal publications related to immuno-oncology (Fig. 8). Key observations/takeaways from this co-occurrence analysis (Fig. 8) are:

- Immune checkpoint-based therapies appear to co-occur the most with lung cancer followed by comparable co-occurrences with liver, breast, colon, and kidney cancer and to the least extent with head & neck cancer. Both PD-1 and PD-L1 co-occur twice as many times with lung cancer as compared to breast cancer, the second most co-occurring type of cancer (Fig. 8). This high co-occurrence can be attributed to the discovery of PD-1/PD-L1 inhibitors as effective treatment for NSCLC.[68-70] CTLA-4 shows a slightly higher degree of overlap with lung cancer as compared to other solid tumors. Other inhibitory immune checkpoint molecules such as IDO, B7-H3, LAG3, A2AR, TIGIT, BTLA, VISTA and TDO appear to have similar co-occurrences with the identified emerging solid cancer types. Other immune check point molecules (sometimes considered stimulatory) such as CD27, CD38, CD47, CD137 and CD278 (Fig. 8) exhibited similar degree of co-occurrences with emerging solid tumors. Immune checkpoint molecules (both inhibitory and others/stimulatory) show no particular preferences for liquid tumors except for CD38 with multiple myeloma (MM) and acute myeloid leukemia (AML) (Supplementary Fig. 8).

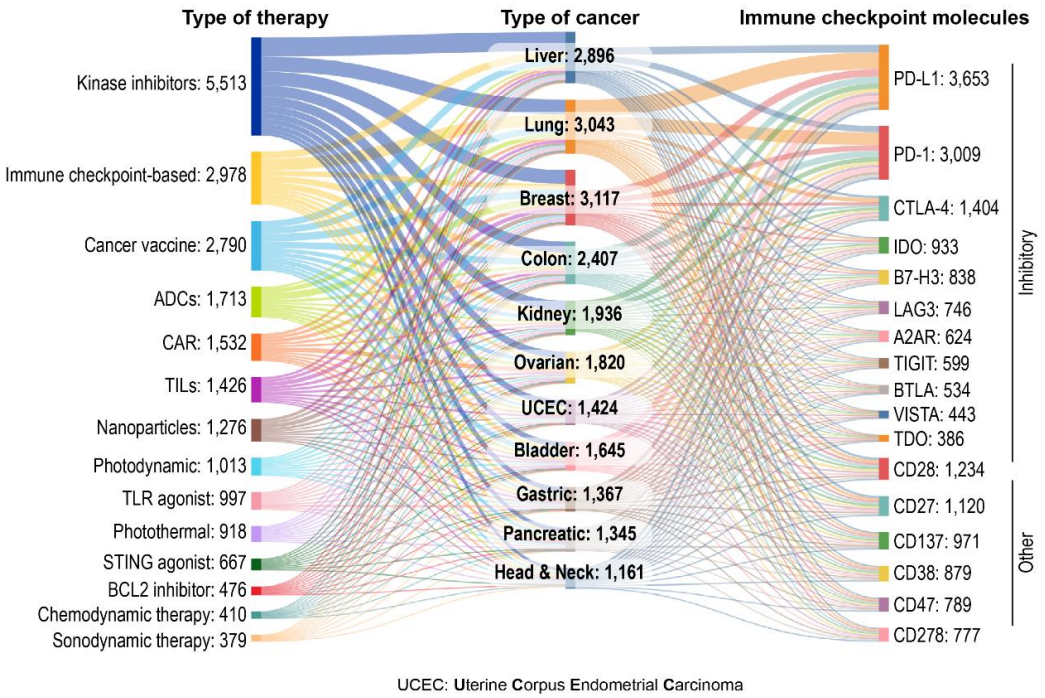

Fig. 8 | Sankey plot indicating co-occurrences of therapies (left) and types of cancer (center), and types of cancer (center) with specific immune checkpoint molecules (right) in journal publications. Data includes journal publications from the CAS Content Collection for the period 2000-2022. Abbreviations: ADCs – **A**ntibody-**D**rug **C**onjugates, CAR – **C**himeric **A**ntigen **R**eceptor, TILs – **T**umor **I**nfiltrating **L**ymphocytes, TLR – **T**oll-**l**ike **R**eceptor, BCL2 – **B**-**c**ell **L**ymphoma **2**, UCEC – **U**terine **C**orpus **E**ndometrial **C**arcinoma.

- Unsurprisingly, ADCs show the greatest overlap with breast cancer (Fig. 8) and this can be attributed to the development and approval of ado-trastuzumab emtansine (T-DM1/Kadcyla),[71] trastuzumab deruxtecan (T-DXd/Enhertu),[72] and sacituzumab govetican (SG/Trodelvy)[73] for the treatment of breast cancer. This is followed closely by co-occurrences of ADCs with lung cancer indicating increased traction.[74] Trastuzumab Deruxtecan (DS-8201a, T-DXd) became the first ADC to gain US FDA approval for the treatment of lung cancer in 2022.[75]
- Cancer vaccines correlate more with liver, lung, breast, and colon cancer as compared to other types of cancer.
- Kinase inhibitors correlate with lung, liver, and breast cancer over most of the other types (Fig. 8).
- CARs show the highest co-occurrence with ovarian cancer. While originally most effective against hematological malignancies, in recent years there has been increasing push towards use of CAR-T for solid tumors with a lot of research focused around ovarian cancer perhaps accounting for this trend.[76,77]
- TLR agonists, BCL2 inhibitors, and STING agonists display similar degrees of co-occurrences with various types of solid tumors.
- Pharmaceutical nanoparticles, often utilized to deliver anti-cancer drugs, appear to show a slightly higher degree of overlap with breast cancer as compared to the rest.
- Therapies such as photodynamic, photothermal, sonodynamic, and chemodynamic appear to show no particular preference for types of cancer.

- In terms of liquid tumors, almost all the selected therapies show equal co-occurrences with the 4 types of emerging liquid tumors except for cancer vaccine which appears to show a slight preference for AML and MM as compared to acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) and kinase inhibitors for ALL and AML (Supplementary Fig. 8).

Our substance database, CAS Registry™[78],consists of >204 million substances indexed based on a host of information including substance roles (>35 unique roles), substance classes, including small molecules, protein/peptide sequences, polymers, nucleic acids, etc., CAS index terms, and CAS registry numbers. Listed below are our observations from analysis of data from >3.2 million substances in the field of immuno-oncology for the period 2012-2022:

- On the whole the number of substances associated with patent publications (~3.1 million) is significantly higher than those associated with journal publications (~133K) being over 20X higher (Fig. 9).
- Therapeutic substances of both small molecules and protein/peptide sequences associated with journal publications in the field of immuno-oncology show a steady growth since 2012, with a sharp increase in small molecules post 2020 (Supplementary Fig. 9a).
- For therapeutic substances associated with patent publications protein/peptide sequence of substance class are 2X that of small molecules (Fig. 9b donut chart) suggestive of greater commercial interest in development of cancer immunotherapeutics with proteins/peptides.
- Co-occurrence analysis of substances with specific emerging concepts using CAS indexed terms with an emphasis on small molecule and protein/peptide sequences (Fig. 9) indicate the following:
    - Therapeutic targets such as T cells, immune checkpoint molecules, B cells, tyrosine kinase, and HER2 appear to lead across both patent and journal publications.
    - For journal publications: (1) therapeutic targets of low co-occurring frequency (<100) with substances include HPK, CSF-1R, ARG1, NPM1, FAP, ILC, TBK1, GPC3, CEACAM5, nectin-4, TROP2, CDC20, among a few others (Fig. 9); (2) therapeutic targets exhibiting sharp upward growth trends (most noticeably in 2022) in co-occurring frequency with substances include dendritic cells, CAFs, TAMs, STING, gasdermins, CDC20, TROP2, LILRB1, TBK1, PKM2, PKB, NEK2, and ARG1 (highlighted in Supplementary Fig. 9c).
    - For patent publications: While the overall number of protein/peptide sequences is 2X that of small molecules – this phenomenon was not uniform across identified emerging therapeutic targets. The protein/peptide sequence to small molecule ratio sheds light on possible commercial interests (Supplementary Fig. 10). For instance, therapeutic targets such as T cells, PCSK9, dendritic cells, MHC and LILRB1 shows an overwhelmingly high co-occurrence with protein/peptide sequences. Targets such as RAD51, FAP and TRK co-occur with protein/peptide sequences and small molecules to an equivalent extent.

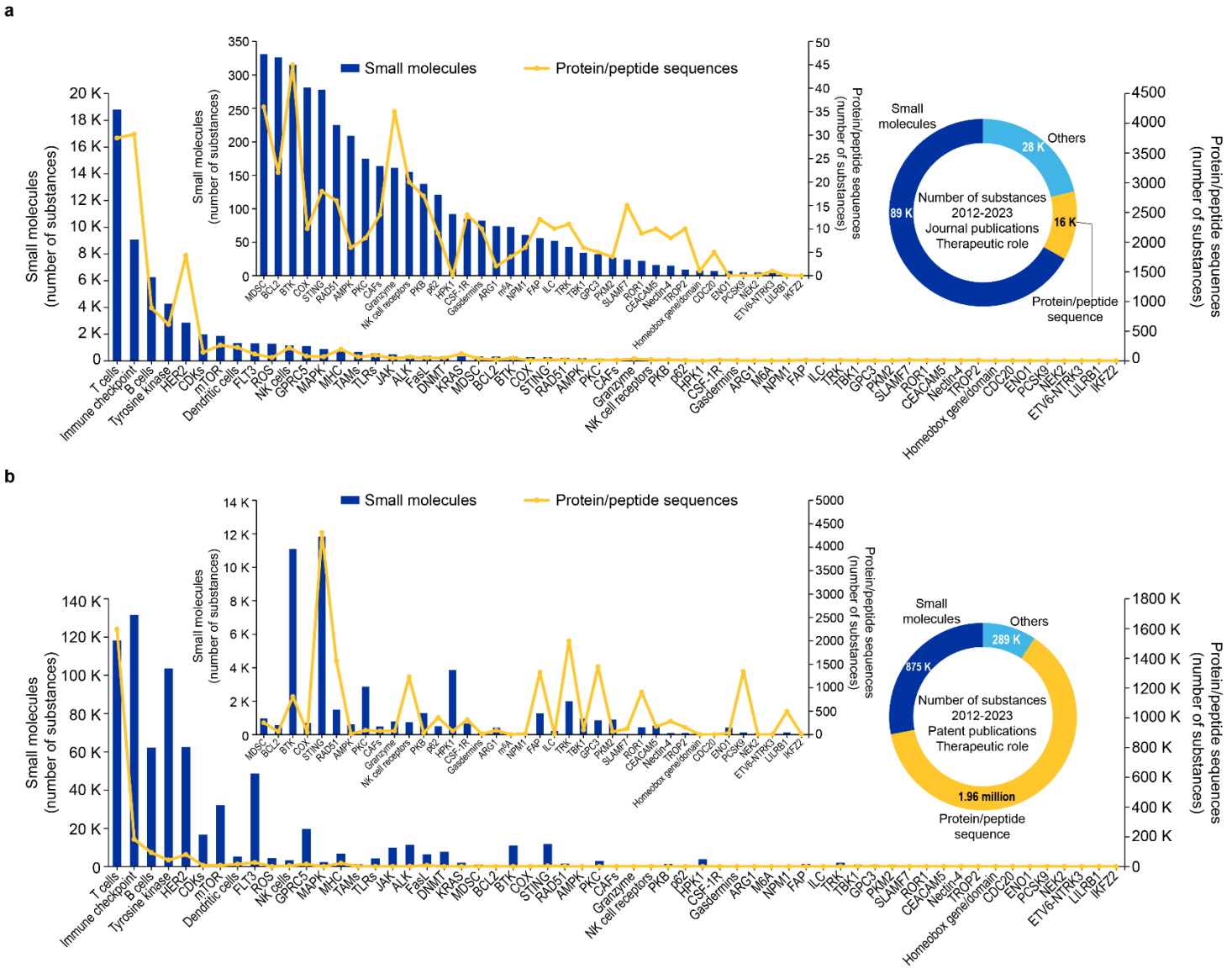

Fig. 9 | Trends from substance data analysis on data retrieved from CAS Registry associated with selected emerging targets in **a**, journal and **b**, patent publications for the period 2012-2022 focused on the two major substance classes – small molecules (blue colored bars) and protein/peptide sequences (yellow line). Inset donut charts depict overall distribution across substance classes. Only substances indexed as therapeutic (THU) were included in the analysis.

Current overview of immuno-oncological therapeutics in development

Data retrieved from Pharmaprojects[79] about drugs currently in the developmental pipeline indicates a steady increase since 2012 (Supplementary Fig. 11a) with a vast majority of drugs in pre-clinical stages or early stages of clinical trials (phases I and II). These drugs are distributed across a wide range of therapeutic classes such as antibodies, gene therapy, vaccines, etc. (Supplementary Fig. 11b). The United States and China are the leaders in this developmental effort - with a majority of the leading companies that are currently conducting research in immuno-oncology based in the US or China (Supplementary Fig. 11c). Key players in this commercial driven research are highlighted in Supplementary Fig. 11c and include well-known pharmaceutical companies such as Bristol-Myers Squibb, Roche, Merck, Sanofi, and AstraZeneca among others. Areas of interest include protein targets such as immune checkpoint molecules, KRAS, interleukins, kinases, chemokines, and cellular targets such as T cells and NK cells (Supplementary Fig. 11d).

Therapies in the development pipeline

Immune checkpoint molecules: Continued interest in development of drugs

Cancer cells employ various strategies such as attracting regulatory T (T_{reg}) cells, reducing the expression of tumor antigens, triggering T cell tolerance or apoptosis, and generating immune suppressing cytokines. The immune suppressing cytokines may activate inhibitory immune checkpoints resulting in a high immunosuppressive tumor microenvironment (TME).[80] Immune checkpoint molecules balance between pro-inflammatory and anti-inflammatory signaling, functioning as key regulators of immune responses to aid the immune system in recognition and elimination of malignant cells. They are further classified into inhibitory or stimulatory/other checkpoint molecules (Fig. 2).

ICIs such as monoclonal antibodies work by blocking the effects of inhibitory pathways and allow T cell activation. ICIs targeting CTLA4, PD-1, PD-L1, and LAG3 have been approved by the US FDA since 2011 (Table 1), totaling eleven compounds, four of which were approved in the past 2 years. Anti-CTLA4, anti-PD-1, anti-PD-L1, and anti-LAG3 agents are utilized in the treatment of multiple solid and hematologic malignancies; however, one of their biggest caveats is that their effectiveness is restricted to only a specific subset of patients. The newest approved category, anti-LAG3 agents, received their first US FDA approval in March 2022. Opdualag, a fixed-dose combination of the LAG3 blocking antibody relatlimab and the PD-L1 inhibitor antibody nivolumab, has been approved for the treatment of unresectable or metastatic melanoma.[81]

Stimulating ICs hold great therapeutic promise – urelumab and utomilumab (PF-05082566) are two anti-CD137 antibodies under development[82] that appear promising in renal cell carcinoma and colon cancer among many others because they can stimulate cytotoxic T cells and enhance the production of interferon gamma (IFN-γ), which is crucial for anti-cancer effects. CD38 plays a role in suppressing immune responses mediated by IFNγ[83] and is expressed on M1 macrophages, as well as in immune responses involving neutrophils and T cells. Daratumumab (Darzalex, Janssen Biotech Inc.),[84] an anti-CD38 IgG1 antibody specific to humans, has received US FDA approval[85] for use either on its own or in combination therapies to treat relapsed or refractory multiple myeloma[86] and is effective at inducing both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity against multiple myeloma cells.[87]

Table 1 | Selected US FDA-approved immune checkpoint inhibitors (ICIs), CAR-T cell therapies, antibody-drug conjugates (ADCs) and cancer vaccines.

Name	Target/ Type	Year of approval	Company	Disease indication	CAS REG number
Immune checkpoint inhibitors (ICIs)					
Ipilimumab/Yervoy	CTLA-4	2011	Bristol Myers Squibb	Melanoma, RCC, CRC, HCC, NSCLC, MPM, EC	477202-00-9
Tremelimumab/Imjudo	CTLA-4	2022	AstraZeneca	HCC	745013-59-6
Pembrolizumab/Keytruda	PD-1	2014	Merck	Melanoma, NSCLC, HNSCC, cHL, PMBCL, Urothelial carcinoma, CRC, Gastric cancer, EC, CC, HCC, MCC, RCC, Endometrial cancer, TMB-H cancer, cSCC, TNBC, PMBCL	1374853-91-4
Dostarlimab/Jemperli	PD-1	2021	GlaxoSmithKline	Endometrial cancer, dMMR solid tumors	2022215-59-2
Retifanimab/ Zynyz	PD-1	2023	Incyte	MCC	2079108-44-2
Durvalumab/Imfinzi	PD-L1	2017	AstraZeneca	NSCLC, SCLC, BTC, HCC	1428935-60-7
Avelumab/ Bavencio	PD-L1	2017	EMD Serono	Urothelial carcinoma, MCC	1537032-82-8
Relatlimab/Opdivo	LAG3	2022	Bristol Myers Squibb	Melanoma	1673516-98-7
CAR-T cell therapy					
Tisagenlecleucel/ Kymriah	CD19	2017	Novartis	B-cell ALL, B-cell NHL	1823078-37-0
Axicabtagene ciloleucel/ Yescarta	CD19	2017	Kite Pharma/ Gilead	B-cell NHL, Follicular lymphoma	2086142-87-0
Brexucabtagene autoleucel/ Tecartus	CD19	2020	Kite Pharma/ Gilead	B-cell ALL, MCL	2691112-12-4
Lisocabtagene maraleucel/ Breyanzi	CD19	2021	Juno Therapeutics, Bristol-Myers Squibb	B-cell NHL	2099722-39-9
Idecabtagene vicleucel/Abecma	BCMA	2021	Celgene Corporation, Bristol-Myers Squibb	Multiple myeloma	2306267-75-2
Ciltacabtagene autoleucel/Carvykti	BCMA	2022	Janssen Biotech	Multiple myeloma	2641066-71-7

Antibody-drug conjugates (ADCs)					
Trastuzumab emtansine/ Kadcyla	HER2	2013	Genentech, Roche	Metastatic HER2-positive breast cancer	1018448-65-1
Inotuzumab ozogamicin/ Besponsa	CD22	2017	Pfizer	CD22-positive ALL	635715-01-4
Loncastuximab tesirine-lpyl/Zynlonta	CD19	2021	ADC Therapeutics	Large B-cell lymphoma	1879918-31-6
Tisotumab vedotin-tftv/ Tivdak	Tissue Factor	2021	Seagen	Recurrent or metastatic CC	1418731-10-8
Mirvetuximab soravtansine/Elahere	FRα	2022	ImmunoGen	Platinum-resistant ovarian cancer	1453084-37-1
Cancer vaccines					
BCG Live	Fibronectin receptors	1990	Organon Teknika Corp.	Bladder cancer	2223648-65-3
Oncophage/Vitespen	Heat shock protein peptide complex HSPPC-96-based vaccine	2008 (approved in Russia)	Antigenics (now Agenus)	Kidney cancer, Metastatic melanoma, and Glioma	492448-75-6
Provenge/Sipuleucel-T	Dendritic cell vaccine	2010	Dendreon Pharmaceuticals	Asymptomatic or Minimally symptomatic HRPC	917381-47-6
Talimogene laherparepvec/T-VEC/Imlygic	Live attenuated HSV1 virus	2015	Amgen, BioVex	Stage IIIb-IVM1c melanoma	1187560-31-1

Abbreviations: ALL – **A**cute **L**ymphoblastic **L**eukemia; BTC – **B**iliary **T**ract **C**ancer; CC – **C**ervical **C**ancer; cHL – **C**lassical **H**odgkin **L**ymphoma; CRC – **C**olo**r**ectal **C**ancer; cSCC – **C**utaneous **S**quamous **C**ell **C**arcinoma; EC – **E**sophageal **C**ancer; HCC – **H**epatocellular **C**arcinoma; HNSCC – **H**ead and **N**eck **S**quamous **C**ell **C**ancer; HRPC – **H**ormone-**R**efractory **P**rostate **C**ancer; MCC – **M**erkel **C**ell **C**arcinoma; MCL – **M**antle **C**ell **L**ymphoma; MPM – **M**alignant **P**leural **M**esothelioma; NHL – **N**on-**H**odgkin's **L**ymphoma; NSCLC – **N**on-**S**mall **C**ell **L**ung **C**ancer; PMBCL – **P**rimary **M**ediastinal **L**arge **B**-cell **L**ymphoma; RCC – **R**enal **C**ell **C**arcinoma; SCLC – **S**mall **C**ell **L**ung **C**ancer; TMB-H – **T**umor **M**utational **B**urden-**H**igh; TNBC – **T**riple **N**egative **B**reast **C**ancer

CAR T-cell therapy: Important cellular immunotherapy

Chimeric antigen receptor T cells or CAR-T cells – engineered cytotoxic T cells that express synthetic CAR receptors[88] – has been of continued interest to the scientific community since their onset. Our trend landscape analysis (Fig. 2) indicates continued growth of publications for CAR therapies (CAR-T, CD19 CAR, CAR-NK). Chimeric receptors combine antigen recognition and T cell binding capability in a single receptor. The receptor portion of CARs consists of four prominent segments – an extracellular domain derived from the single chain variable fragment (sc-Fv) of the antibody, which is responsible for tumor antigen recognition, a hinge region that connects the sc-Fv fragment to the transmembrane (TM) domain, and the intracellular signaling domain. The hinge region and the TM domain anchor CARs to the cell membrane and help in the downstream signaling cascade for T cell activation.[89]

CAR-T cells are created by harvesting T cells from the patient's blood, genetically modifying them to target cancer cells specifically, and multiplying their numbers. These modified cells are then reintroduced into the patient's bloodstream to attack the cancer cells. CAR-T cells have shown promising results in treating hematological cancers, such as acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma (NHL), and multiple myeloma.[90-92] Kymriah (tisagenlecleucel) was the first US FDA-approved CAR-T cell therapy developed by Novartis.[93] This CD19-directed therapy was approved in 2017 for the treatment of B-cell acute lymphoblastic leukemia (ALL). To date, five more CAR-T cell therapies have been approved by the US FDA (Table 1). While CAR-T cell therapy has shown remarkable success in treating hematological cancers,[94] their use in solid tumors such as gastric,[95] pancreatic,[96] and lung cancer[97] is still in exploratory stages. The challenge of using CAR-T immunotherapy in solid tumors arises from a lack of suitable CAR-T antigens and the tumors' immune-suppressive and complex microenvironment which poses difficulties in the trafficking of CAR-T cells.[98] Current research is focused on improving infiltration of solid tumors by administering CAR-T-based therapy directly to the tumor site rather than through the bloodstream. To date, >1,100 trials for CAR-T therapies are ongoing,[99] of which ~150 are directed towards solid tumors.[100,101] In recent years, CAR-NK and CAR-M therapies are being developed as alternate/synergistic therapies for solid tumors.[102]

Despite its effectiveness, CAR-T therapies have disadvantages such as heightened immune reactions including cytokine release syndrome, CAR T cell-related encephalopathy syndrome, off-tumor toxicities, and immune effector cell-associated neurotoxicity syndrome.[90,103] Another major concern is the high cost of therapy. However, various efforts are being made to counter the drawbacks of CAR-T therapy such as optimizing autologous CAR-Ts for liquid tumors,[104] expanding CAR administering facilities and developing next-generation CAR T-cell therapies.

Antibody-drug conjugates: Effective and promising “magic bullets”

ADCs are among the most promising drug classes in oncology, currently, with the development accelerating in the last 20 years. An ADC is composed of a monoclonal antibody and a cytotoxic payload connected with a linker to create a targeted immunoconjugate.[16] Despite being proposed in the early 1900s by Paul Ehrlich as a “magic bullet” that targets pathogens,[105] it was not until the 1980s that ADCs were first explored in clinical trials with the first ADC gaining US FDA approval in the year 2000.

Optimization and selection of antibodies, linkers, and payloads has helped fuel accelerated ADC development. Ideal antibody characteristics include selective binding and high

affinity for the target antigen, a long half-life, low immunogenicity, and superior linker binding.[106] Currently, ADCs widely use the immunoglobulin G1 antibody.[107] Recent advances in antibody engineering research has offered new alternatives and include bispecific and trispecific antibodies targeting two and three distinct antigens[108] and also nanobodies, single domain antibody fragments.[109] The linker moiety of an ADC should be stable in plasma, not alter the characteristics of the antibody or drug, be hydrophilic to mitigate lipophilic payload solubility effects, and release the payload selectivity and completely.[110] They are divided into two major classes, cleavable and non-cleavable with cleavable linkers dominating both approved ADCs and ADCs currently in clinical trials.[111] Lastly, the payload used for ADCs must also be stable in both blood and plasma and needs to be highly potent in small doses due to their selective release.[112] A range of payloads are currently being used in approved ADCs including suristatins, calicheamicin, duocarmycins, maytansinoids, and pyrrolobenzodiazepines, with payloads such as amberstatin, eribulin, and tubulysin currently researched in clinical trials.[113]

Over 150 unique ADC candidates are being researched in clinical trials with their most utilized target antigens being HER2, followed by TROP2, Claudin 18.2, cMET, and B7H3, respectively. Eight unique bispecific ADCs have also entered clinical trials for the treatment of various solid tumors.[16] Among the various payloads utilized, topoisomerase I inhibitors, which impact DNA replication in cancer cells, are currently utilized by over 40 ADC candidates in clinical trials. Fifteen ADCs have gained regulatory approval across a wide range of cancer types including solid tumors such as breast, gastric and ovarian as well as hematologic malignancies such as lymphoma and leukemia.[16] Table 1 showcases a few promising regulatory approved ADCs to highlight the diversity amongst target antigens, disease indications, companies, and regulatory approval dates.

Cancer vaccines: Beneficial preventive strategy

Cancer vaccines are a form of immunotherapy aimed at harnessing the body's immune system to fight against cancer cells by reprogramming the immune system and activating T cell mediated adaptive immune response to attack 'foreign' cancer cells.[114] Cancer vaccines are capable of targeting either tumor surface antigens (TSAs) or tumor-associated antigens (TAAs) – TSAs are proteins unique to cancer cells that are not expressed in healthy cells,[114,115] TAAs on the other hand are expressed in normal as well as cancer cells to differing extents – higher expression levels in cancer cells make them suitable targets for developing cancer vaccines.[116] Cancer vaccines can either be administered as 'preventive' aids or as 'therapeutics' to prevent the occurrence of tumors or cure the disease, respectively. Examples of the former include: Cervarix (GlaxoSmithKline Biologicals),[117] Gardasil-4 (Merck & Co.), Gardasil-9 (Merck Sharp & Dohme LLC),[118] and Hepatitis B (HBV) vaccine (HEPLISAV-B, Dynavax Technologies Corporation)[119]; examples of the latter include: Bacillus Calmette-Guerin (BCG)[120] and Provenge (sipuleucel-T; Dendreon Pharmaceuticals, LLC).[121] Table 1 highlights a few selected cancer vaccines with respect to their targets, disease indications, companies, and regulatory approval dates.

Below are a few types of therapeutic cancer vaccines depending on the design strategy and the mode of action:

1. **Peptide vaccines**: These vaccines contain small fragments of cancer-specific peptides derived from either TSA or TAA containing T cell epitopes.[122] When injected into the body,

they elicit an immune response that targets cancer cells expressing these peptides e.g., HBV and HPV vaccines.

2. **Whole-cell vaccines**: Whole-cell vaccines use whole tumor cells or cell lysates typically modified/treated to enhance their ability to trigger an immune response. Aimed to elicit stronger and more diverse immune reaction[123,124] by presenting a broad range of tumor antigens. Provenge (sipuleucel-T; Dendreon Pharmaceuticals, LLC)[121] is the first FDA-approved dendritic cell vaccine, a type of whole-cell vaccine.[125]
3. **Virus-based/Oncolytic vaccines**: Viruses, engineered to carry cancer-specific antigens, trigger immune response against cancer cells expressing those antigens upon administration.[126,127] Nadofaragene firadenovec-vncg (Adstiladrin; Ferring Pharmaceuticals A/S)[128] is a 2022 US FDA-approved non-replicating adenoviral vector-based therapy for treating adults with high-risk BCG unresponsive non-muscle invasive bladder cancer with carcinoma in situ with/without papillary tumors.[129] Oncolytic viral therapy relies on viruses that kill cancer cells without harming normal cells[127] and is the basis for the development of the US FDA-approved talimogene laherparepvec (T-VEC or Imlygic; BioVex Inc.)[130] used for treatment of melanoma utilizing herpes simplex virus type 1.
4. **Nucleic acid vaccines**: Genetic material (DNA) encoding specific cancer antigens are introduced into the patient's cells leading to expression of said antigens eliciting an immune response against the cancer. DNA vaccines for cancer immunotherapy are under clinical trials (e.g. NCT04090528, NCT03199040 and NCT04251117). mRNA-based vaccines are currently in development and are undergoing clinical trials (e.g. NCT04382898 and NCT03164772) gaining importance in cancer immunotherapy.[131] Nucleic acid vaccines are safe, low/non-immunogenic, potent, fast acting, and easier to manufacture.[132]
5. **Nanovaccines**: Nanocarriers encapsulating antigens thereby preventing their degradation are being used to treat cancers and infectious diseases such as COVID-19. Given their small size, the use of adjuvants along with target antigens help in their successful delivery to antigen presenting cells.[133]

A closer look at our data indicates that the number of publications related to cancer vaccines in immunotherapy have grown at a modest rate over 2020-2022 (Figs. 2 and 7). Amongst the various types of cancer vaccines, RNA-based and nanovaccines have grown the fastest in the last three years (Fig. 2).

Natural killer (NK) cells: Promising cancer immunotherapeutics

Natural Killer (NK) cells, a type of cytotoxic lymphocyte, play a critical role in the immune system's surveillance and elimination of cancer cells. Given their potent antitumor activity, NK cells are being actively explored as viable targets in cancer immunotherapy in several ways:

1. Adoptive cell therapy (ACT): ACT involves isolating and expanding NK cells from a patient's own blood (autologous) or from a donor (allogenic), followed by their infusion back into the patient.[134-136] The initial use of NK cells in treating cancer involved infusing IL-2-activated cells into patients in the 1980s.[137] However, efficacy was limited due to IL-2 toxicity and unknown factors such as the impact of T_{reg} cells. Later, evidence in 2002 indicated the clinical benefit of NK cells in patients receiving bone marrow transplants,

showing lower relapse rates in certain conditions.[138] Various trials involving adoptive cell transfer of activated NK cells demonstrated some success, especially when there was evidence of the cells persisting and expanding post-infusion.[136,139] Recent studies have shown promise in enhancing NK cell efficiency by pre-activating them with a combination of cytokines, resulting in improved functions both in vitro and in vivo in mouse models of cancer.[140,141]

2. Engineered NK cells: Recent research has shown achievements through the use of engineered NK cells containing activating chimeric antigen receptors (CARs) designed for targeting tumor-specific antigens.[142] When CAR-NK cells developed from umbilical cord blood transduced with a modified retroviral vector expressing genes for an inducible caspase-9 suicide switch, an anti-CD19 CAR, and IL-15 were used to treat patients with CD19+ conditions, they exhibited favorable expansion, long-lasting presence, and positive outcomes, with no significant adverse effects observed[143].

3. Combination therapies: NK cell-based therapies are often used in combination with other immunotherapies, such as immune checkpoint inhibitors or monoclonal antibodies, to enhance their efficacy[144] by overcoming tumor immunosuppression and promoting more robust antitumor immune responses. Typical immune checkpoint PD-1/CTLA-4 inhibitors have been used not only in relieving the inhibitory state of T cells but also to reverse the incapacity of NK cell.[145]

4. Targeting inhibitory receptors: Strategies are being explored to block or downregulate inhibitory receptors on NK cells, such as NKG2A, to overcome tumor-induced immunosuppression and enhance NK cell activity.[146]

Despite their great promise challenges remain in NK cell-based immunotherapy, including optimizing NK cell expansion and persistence, improving homing to tumor sites, and overcoming immunosuppressive tumor microenvironments. Ongoing research and clinical trials are aimed at addressing these challenges and further unlocking the therapeutic potential of NK cells in cancer treatment. A few of these clinical trials are listed in Table 2 to show a snapshot of this currently active clinical trial landscape.

Table 2 | Selected clinical trials involving NK cell-based therapy.

NK cell strategy	Indication	Intervention	Status	Sponsor	Clinical trial ID
Engineered NK cells	Ovarian cancer	Natural killer Group 2D CAR-NK Cells	Recruiting	Hangzhou Cheetah Cell Therapeutics	NCT05776355
Combination therapy	HER2 breast cancer	Allogenic NK cells and Trastuzumab and Pertuzumab	Recruiting	Vall d'Hebron Institute of Oncology	NCT05385705
Combination therapy	Neuroblastoma	Hu3F8 (Anti-GD2 Antibody) and allogeneic NK cells	Active	Memorial Sloan Kettering Cancer Center	NCT02650648
Targeting inhibitory receptors and combination therapy	HL or NHL	AFM13-NK and AFM13 monoclonal antibody	Active	M.D. Anderson Cancer Center	NCT04074746

Abbreviations: HL – **H**odgkin's **L**ymphoma; NHL – **N**on-**H**odgkin's **L**ymphoma

Tumor-associated macrophages (TAMs): Reprogramming the tumor microenvironment

Tumor-associated macrophages (TAMs), a type of immune cell that infiltrates the tumor microenvironment and plays a crucial role in tumor progression and immunosuppression, are derived from circulating monocytes that recruited to the tumor site by various chemokines and cytokines produced by the tumor cells.[147] Generally, TAMs can be classified into two main phenotypes: M1 and M2.[148] The M1 phenotype, also known as classically activated macrophages, is associated with pro-inflammatory responses and antitumor activity. In contrast, the M2 phenotype, also called alternatively activated macrophages, exhibits anti-inflammatory properties, and promotes tumor growth, angiogenesis, tissue remodeling, and immunosuppression.[148] Listed below are ways in which TAMs are currently being explored in cancer immunotherapy:

1. **CAR-M cells**: Engineered cells with edited CARs to identify specific antigens on cancer cells, enhancing their ability to recognize and engulf these cells by presenting tumor antigens to Th1 cells leading to the production of anti-inflammatory factors, which in turn activate T-cell mediated immunity. Carisma Therapeutics is currently recruiting patients for an early phase I study of their engineered HER2 targeted CAR-M cell therapeutic CT-0508 (NCT04660929). CT-0508 will be studied in combination with the ICI pembrolizumab for the treatment of HER2 overexpressing solid tumors.[149]
2. **Repolarization of TAMs**: The goal is to shift TAMs from the M2 phenotype to the M1 phenotype, exploiting the pro-inflammatory responses and antitumor activity of M1 macrophages and can be achieved by using specific molecules or drugs that modulate the macrophage polarization state[150-152] thereby promoting antitumor immune responses.[153]
3. **Depletion of TAMs**: Reducing the number of TAMs within the tumor microenvironment by targeting specific surface markers or by blocking the recruitment of monocytes to the

tumor site appears to be a potentially viable approach.[154] This strategy is being studied for the treatment of platinum-resistant epithelial ovarian cancer (NCT05053750). The TAM targeting therapeutic, zoledronic acid, a bisphosphonate drug, blocks the mevalonate pathway causing macrophage apoptosis and depletion[155] in combination with paclitaxel and bevacizumab.

4. **Inhibition of TAM-associated signaling pathways**: TAMs can secrete various immunosuppressive factors and cytokines that promote tumor growth and immunosuppression. Targeting these signaling pathways, such as colony-stimulating factor 1 receptor (CSF-1R), can inhibit TAM recruitment and function.[156] The M.D Anderson Cancer Center is currently researching this strategy consisting of a combination of TAM depletion and inhibition of TAM-associated signaling in the above mentioned active early phase I clinical trial NCT05053750.

By targeting TAMs, researchers aim to reprogram the tumor microenvironment to promote an immune-activating and tumor-suppressing environment. However, it's important to note that TAMs' role in cancer is complex and context-dependent, and further research is needed to better understand their diverse functions and develop effective TAM-targeted therapies.

Modes of delivery: Optimized targeting via smart carriers

To improve the efficacy of targeted immunotherapy and reduce off-target adverse effects, drug or cell delivery systems precisely delivering therapeutic agents to the tumor microenvironment have been widely applied.[157,158] The advantages of using drug delivery systems are obvious and manifold: delivery of multiple agents simultaneously, enabling synergistic effects,[159] enhancing pharmacokinetics by improving the stability and half-life, highly specific targeting achieved via functionalization with targeting ligands that recognize specific biomarkers on cancer cells or immune cells.[160]

Frequently used delivery systems include nanoparticles, cell-based and exosome-based delivery systems, biomaterial-based implants, and injectable hydrogels and scaffolds. With attractive tunable size and surface properties, nanocarriers can increase the delivered drug's overall therapeutic index that are either encapsulated or conjugated to the surfaces of nanoparticles. Materials such as lipids, metals, polymers, and others have been applied (Fig. 10). Clinical research has demonstrated that a significant proportion of cancer patients exhibit insensitivity to immunotherapy, mostly because of the immunomodulatory exchanges between tumor cells and the immunosuppressive tumor microenvironment, managing the immune tolerance of tumors. Significant efforts have been concentrated on introducing nano-sized carriers to cancer medicine.[161] Targeted remodeling of the immunosuppressive tumor microenvironment using appropriately engineered nanoparticles provides a favorable strategy for enhancing the effectiveness of tumor immunotherapy[160,162] and help to overcome immune tolerance of tumors.[163]

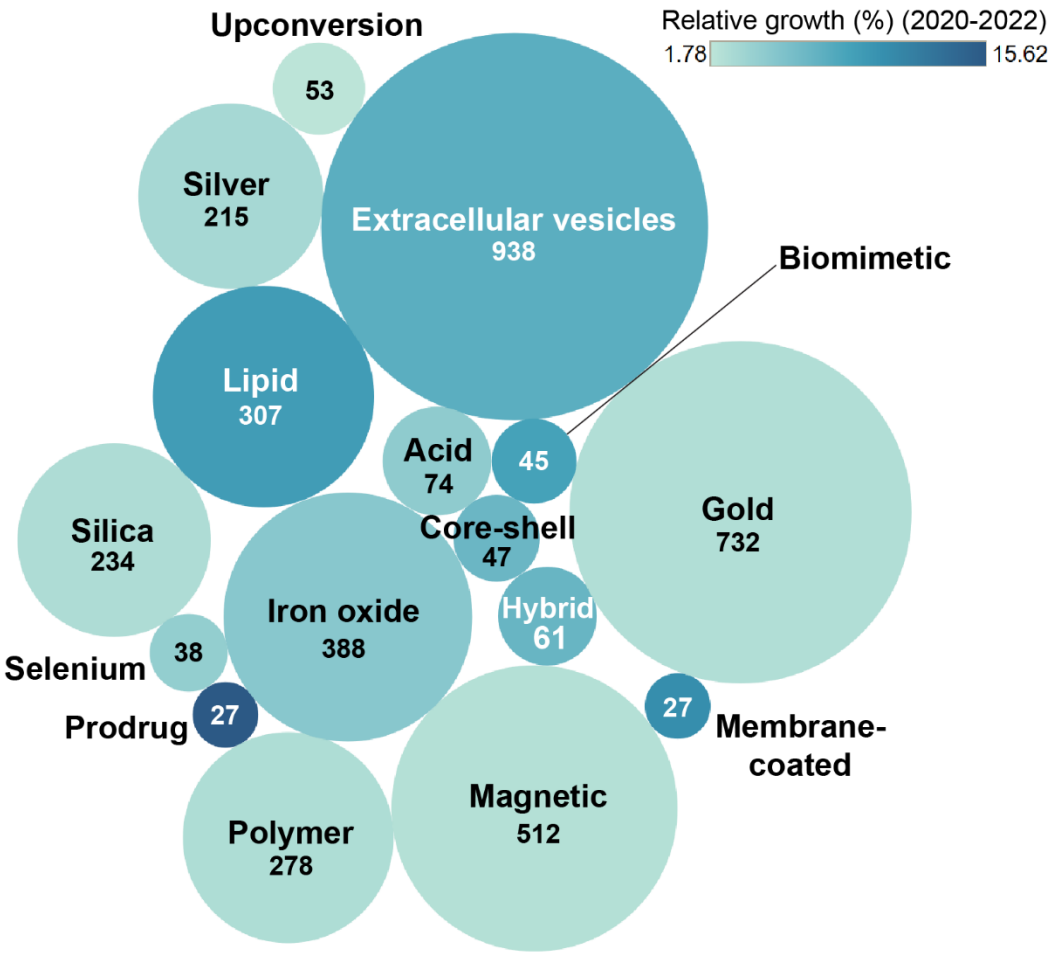

Fig. 10 | Distribution of drug delivery vehicles used in cancer immunotherapy. The size of the circles reflects the number of publications in the CAS Content Collection for the period 2000-2022 related to the delivery vehicle type. The color intensity reflects the relative publication growth rate for the last three years (2020-2022).

1. Nanoparticles (NPs)

Broadly speaking, nano-drug delivery systems can be divided into: (1) passive targeting, transported to target sites through regular physiological processes with carriers including emulsions, liposomes, microcapsules, or microspheres; (2) active targeting carriers, the surfaces of which have been modified with specific ligands to enable binding to receptors on the target cells or organs; (3) physical and/or chemical targeting carriers directed by external forces such as temperature, pH, or magnetic field.

Pharmaceutical nanocarriers can be prepared from lipids, polymers, metals, inorganics, and other materials. Nano-medicines target tumors via either passive (also known as the Enhanced Permeation and Retention effect) and/or active mechanisms.[164] Research and development in the field of cancer nanotherapeutics have experienced an exponential growth since early 2000's since the commercialization of the first-generation anti-tumor nanomedicines

including DOXIL (doxorubicin hydrochloride, Baxter)[165,166] and Abraxane (paclitaxel, Bristol Myers Squibb).[167,168]

i. **Lipid NPs**[169] are currently most widely used NPs and exhibit high growth rate as compared to other NPs in the field of cancer immunotherapy (Fig. 2). Lipid-based NPs are superior to other nanosized drug delivery systems in minimizing systemic toxicity while maintaining adequate solubility[170] and are thus the most common type of regulatory approved nanomedicines.[171] They have been applied in drug delivery since the discovery of liposomes in the 1960s, but marked several serious advancements: (i) with the introduction of PEGylation,[172] which increased their circulation half-lives further improving their effectiveness,[173] (ii) with the discovery of the cationic/ionizable liposomes able to deliver anionic nucleic acids,[174] as well as (iii) with the development of the solid lipid nanoparticles and the nanostructured lipid carriers offering higher payload and stability, and largely improved scalability.[175,176] Thus, in cancer immunotherapy, lipid-based NPs could successfully deliver small molecules and mRNA therapies *in vivo* to achieve remarkable antitumor activity.

ii. **Metal NPs.** Inorganic NPs provide an appropriate framework in which multiple modules can be combined to give multifunctional capabilities. Metallic NP formulations are particularly advantageous because of their potential for dense surface functionalization and capability for optical or thermal based therapeutic and diagnostic methods.[177]

iii. **Magnetic iron oxide NPs.** Iron oxide NPs can generate heat when exposed to an alternating magnetic field, a property that has been utilized to induce cell death and stimulate an immune response in hyperthermia-based cancer treatment. Iron oxide NPs can also be used as contrast agents for magnetic resonance imaging, allowing for non-invasive tracking of immune cell migration and infiltration into tumor sites. In order to enhance their cellular uptake and effectiveness, these NPs can be modified with a specific coating, conjugated to drugs, proteins, enzymes, antibodies, or nucleotides, and can be directed to an organ, tissue, or tumor sites using external magnetic field; they can be used in the development of dual-purpose probes for the *in vivo* transfection of siRNA.[178]

iv. **Silver NPs.** Silver NPs known for their antibacterial activity, are also known to enhance the anti-tumor effects of anticancer drugs in combination therapies, allowing use of lower doses to reduce cytotoxic effects and increase efficacy.[179] They can thus operate as direct anti-cancer agents, as well as delivery platforms of various cytotoxic drugs or enhance the anti-cancer performance of combinational partners upon chemo- or radiotherapy.[180] Silver nanoparticles can exhibit a plasmon resonance effect and generate heat when exposed to specific wavelengths.[181] This property can be harnessed for photothermal therapy, where the localized heat generated by the nanoparticles damages cancer cells and stimulates an immune response.

v. **Gold NPs.** Gold NPs are a multifunctional therapeutic modality, performing as targeted delivery systems for vaccines, nucleic acids, and immune antibodies, as theranostic agents, and as tools in photothermal cancer therapy. They have been successfully applied also in medical imaging, such as radiotherapy, magnetic resonance angiography, and photoacoustic imaging. Gold nanostructures including nanoparticles, nanorods, nanocages, etc., are easily synthesizable in diverse shapes and sizes through various chemical, physical, or biological methods, which empowers their manageability, since even minor modifications of their size and shape can produce significant alterations in their functional properties including biodistribution, metabolism, cytotoxicity, and

immunogenicity.[182,183] Similar to silver NPs, gold NPs can be utilized in photothermal therapy via localized plasmon surface resonance.[184]

vi. **Silica NPs.** Mesoporous silica exhibits high porosity, appropriate biocompatibility, and facile surface functionalization. Silica NPs can be engineered to various shapes, sizes, and surface properties, making them versatile tools for targeted drug delivery, imaging, and immunomodulation.[185] After the introduction of sub-micrometer mesoporous silica termed MCM-41[186] and its successful application as a nanocarrier,[187] it has been regarded as a promising drug delivery system. Moreover, mesoporous silica exhibits self-adjuvant property, significantly enhancing anticancer immunity without additional immunomodulators.[188,189] Mesoporous silica has emerged as a prospective nanocarrier for cancer vaccines as well,[190] alleviating antitumor immunity through dual loading of antigen and adjuvant on a single platform.[185]

vii. **Polymeric NPs.** Polymeric nanocarriers are beneficial for immunotherapy approaches because they can be modulated with adequate physical properties, encapsulants, and surface ligands; they can be also tailored to co-deliver multiple therapeutic agents to cancer or immune cells.[191] Various stimuli-responsive (e.g., enzyme-, pH- and redox-responsive) polymers, including natural and synthetic polymers, have been utilized as smart nanocarriers for immunotherapy applications. Redox-responsive polymeric nanohydrogels exhibiting tissue-like mechanical properties and high porosity have been extensively studied and shown to be effective in protecting payloads including protein drugs, gene therapeutics, and small-molecule anticancer drugs in blood circulation, as well as in their targeted release.[192] The most commonly used natural polysaccharides include dextran, polysialic acid, hyaluronic acid, chitosan, and heparin, while polyvinyl pyrrolidone, polyacrylamide, polyvinyl alcohol, polyethylene glycol (PEG), and PEG copolymers such as poloxamines, poloxamers, and polysorbates are preferred synthetic polymers.[191] Smart polymeric nanoparticles have been demonstrated to enhance tumor immunotherapy, to alleviate immunosuppression, and prevent cancer cells from evading the immune system.[191,193]

2. Exosomes

Superior innate stability, low immunogenicity, biocompatibility, and excellent capacity for membrane penetration allow exosomes to be valuable natural nanocarriers for efficient drug delivery.[194] As important mediators of intercellular communications, exosomes are increasingly gaining interest in the context of cancer immunotherapy.[195,196] Exosomes, either tumor-derived, comprising tumor-associated antigens, or derived from dendritic cells presenting antigens, can trigger immune activation and therefore they can be used in developing anti-cancer vaccines.[197] Moreover, tumor-derived exosomes hold information from primary cells and express complexes of MHC epitopes and co-stimulatory proteins, thus they can activate CD8 T-cells, which offer unique therapeutic approaches for developing cancer vaccines.[198,199] Exosomes participate in the formation of the cancer immunosuppressive microenvironment, thus tumor exosome production control might be an effective treatment strategy. Exosomes also play a key role in the PD-1/PD-L1 immune checkpoint inhibitor treatment.

3. Others

A variety of other nanovehicle delivery systems for cancer immunotherapy are found in the CAS Content Collection: prodrug NPs,[200] core-shell NPs,[201,202] hybrid NPs,[203] photon

upconversion NPs,[204] biomimetic NPs,[205] cell membrane-coated NPs,[206] deformable nanoconstructs,[207] stimuli-responsive NPs,[208] etc.

As compared to nanoparticle-mediated, noncovalent drug encapsulation, stimulus-responsive prodrug nanoparticles have a pharmaceutical advantage: they can be tuned to minimize drug leakage and to control drug release profiles through chemical linkers[209,210] and have recently been developed as a strategy to enhance the cancer immunotherapy effectiveness.[200] Iron oxide–zinc oxide core–shell NPs have been successfully used to deliver carcinoembryonic antigen into dendritic cells while simultaneously acting as an imaging agent.[201] Gold-silver core-shell hybrid NPs have been reported to attenuate the tumor cell-promoting activity of cancer-associated fibroblasts, leading to a prominent attenuation of metastatic dissemination *in vivo*.[202] Hybrid NPs comprising of two or more constituents with different compositions and properties, typically organic and inorganic, have been developed, combining the functions of participating materials and exhibiting immense potential in advancing cancer immunotherapy.[203] Upconversion NPs devised for cancer therapy typically have employed photoinitiators and dyes to enhance reactive oxygen species by producing radicals in the tumor site through photodynamic therapy.[204] Use of stimuli-responsive delivery systems can enable spatiotemporal control over drug release.

Biomarkers: The earlier detected the better

Early detection of cancer is critical for reducing its morbidity and mortality.[211,212] Kinases, chemokines, transcription factors, and glycoproteins stand out as key players among the diverse classes of emerging biomarkers for various types of cancers due to their intricate involvement in cancer development, progression, and response to therapy.

In the realm of cancer immunotherapy, certain transcription factors have been recognized for their pivotal roles in orchestrating immune responses and influencing the tumor microenvironment. Research on transcription factors such as ENO1, SETD2, nectin-4, TROP2, gasdermin E (GSDME), TCF-7, and glutathione peroxidase 4 (GPX4) has gathered increased attention in the past three years showing increased growth in journal and patent publications based on the CAS Content Collection (Fig. 2). As understanding of the complex interplay between transcription factors and the immune system deepens, it can be expected that transcription factor-based biomarkers will play an increasingly important role in the quest for precision cancer immunotherapy.

ENO1, a glycolytic enzyme acting as a plasminogen receptor on cell surfaces, contributes to cancer cell proliferation, migration, invasion, and metastasis.[213] ENO1 overexpression has been documented in a broad range of cancers including lung, breast, liver, and others, and is usually associated with poor prognosis. This overexpression can contribute to the metabolic changes associated with cancer cells, as they regularly rely on glycolysis for energy production. In breast cancer, enhanced ENO1 expression has been associated with greater tumor size and a shorter disease-free interval.[214] Patients with lung cancer overexpressing ENO1 also exhibited poor clinical outcomes, with shorter overall survival.[215,216] ENO1 overexpression in hepatocellular carcinoma correlated positively with venous invasion.[217,218] ENO1 overexpression in multiple cancer types, its localization at the cancer cell surface, and its targetability make this protein a rising cancer biomarker and potential target for therapeutic agents.[219]

SETD2 is a gene that encodes an enzyme involved in histone modification, specifically histone H3 lysine 36 (H3K36) methylation. This gene plays a crucial role in epigenetic regulation and has been implicated in various cellular processes, including DNA repair, transcriptional regulation, and chromatin organization. Mutations in SETD2 can be both loss-of-function and gain-of-function mutations, affecting its histone methylation activity. Frequent mutations have been reported in cancers like clear cell renal cell carcinoma,[220] acute lymphoblastic leukemia,[221] glioblastoma,[222] and others. The correlation between SETD2 deleterious mutation and tumor mutation burden has placed it in the spotlight as a promising prognostic biomarker for cancer immune checkpoint inhibitor treatment.[55,223]

The cell adhesion protein nectin-4 also emerges as a favorable prognostic blood-based biomarker and is known to be overexpressed in several cancer types, including breast,[224] ovarian,[225] endometrial,[226] urothelial,[227] and certain subtypes of bladder cancer .[228] High levels of nectin-4 expression have been correlated with more aggressive cancer behavior, poor prognosis, and shorter survival rates, making it also an emerging prognostic biomarker.[229,230] For example, in a multivariate clinical analysis of triple-negative breast cancer survival rate, nectin-4 has been highlighted as a favorable breast cancer prognostic marker.[54]

Gasdermin E (GSDME), also known as DFNA5 (Deafness, Autosomal Dominant 5), is a protein that is involved in programmed cell death, specifically pyroptosis, a form of cell death in response to infection or cellular stress. GSDME has been found highly expressed in most malignant cancers, and an obvious relationship exists between GSDME levels and survival prognosis of cancer patients.[231] Studies have also shown that GSDME methylation is a valuable molecular biomarker in cancer, specifically in breast cancer diagnoses,[232] with a recent report suggesting importance in a variety of other cancer types as well.[233] The prominent expression and methylation properties of GSDME in diverse cancers make it an emerging favorable prognostic biomarker with a tremendous potential.

IGF2BP2, protein belonging to the family of RNA-binding proteins, plays a role in post-transcriptional regulation of gene expression by binding to specific target mRNAs, thereby influencing their stability and translation. While IGF2BP2 is more commonly associated with metabolic functions and type 2 diabetes, it has also been studied in the context of cancer.[234] Its overexpression can lead to the stabilization and increased translation of specific mRNA targets and in some cases can promote tumorigenesis and cancer progression by enhancing the expression of oncogenic genes.[235] In the context of hepatocellular carcinoma, IGF2BP2 overexpression may be linked to cancer development.[236] The expression levels of IGF2BP2 in tumor tissues and its correlation with clinical outcomes are areas of active research.

Tumor mutational burden (TMB) has recently emerged as a significant and independent predictor of ICI treatment response to diverse tumor types. TMB is a measure of number of mutations expressed by cancer cells and can arise due to various factors, such as exposure to environmental carcinogens or errors during DNA replication. Clinical studies have demonstrated that patients with high TMB tend to have better responses to ICIs and improved overall survival rates.[58] These findings have led to the exploration of TMB as a biomarker to guide treatment decisions in immuno-oncology[237] across various cancer types. By assessing a tumor's mutational burden, clinicians can identify patients who are more likely to benefit from ICI therapy, thereby personalizing treatment approaches.[238]

Other biomarkers of apparent prognostic significance include – TROP2 a transmembrane glycoprotein overexpressed in many cancers, including breast, lung, colorectal, pancreatic, and bladder cancers[57]; and LC3B a protein involved in the autophagy pathway. Autophagy is a highly regulated process that plays a critical role in maintaining cellular homeostasis. Higher levels of LC3B expression are associated with better patient outcomes, indicating an advantageous prognostic value.[239]

Conclusions

The field of immuno-oncology has shown continuous and accelerated growth since 2000 with clear signs of further expansion. The success of immunotherapeutic drugs in treatment of hard-to-treat cancers has given patients a new lease on life and speaks to the enormous potential of immuno-oncology. Accelerating interest means the volume of information (in terms of scientific publications) that is becoming available can be overwhelming. Gaining insights from large volumes of data is invaluable in guiding future growth of the field. Achieving this lofty goal though is extremely challenging.

We tackled this challenge using a novel NLP-based approach and created a "Trend Landscape Map". The map is designed to be a comprehensive resource and provides information about emerging concepts in the field of immuno-oncology across various levels – right from a panoramic bird's eye view down to zoomed in views of specific concepts. The intrinsic value of the map has been enhanced by incorporating information about growth and size of the field giving a nuanced view. The four major areas where most of the identified emerging concepts were clustered are: types of targets, therapies, biomarkers, and cancers. Areas where relative growth is considerably higher than the absolute number of publications represent potential lacunae of interest. For example, while immune checkpoint molecules, PD-1 and PD-L1, continue to show steady growth and is supported by the existence of several PD-1 targeted US FDA approved therapeutics, other immune checkpoint molecules such as TIGIT, B7-H3, A2AR, and LAG3 show high relative growths with low absolute number of publications. A few other key areas of emergence worth highlighting are CAR therapy especially CAR-NK and CD19 CAR-T; cancer vaccines especially RNA-based and nanovaccines; lipid-based and membrane-coated nanoparticles as modes of delivery systems. Biomarkers and therapeutic targets in immuno-oncology are closely tied and show a large degree of overlap. A few examples of targetable biomarkers that we identified as emerging include ENO1, nectin-4, TROP2, PCSK9, LILRB1, CEACAM5, and the immune checkpoint molecule TIGIT.

To identify and understand the trends across various emerging concepts in cancer immunotherapy, we have leveraged substance data from CAS Content Collection and CAS Registry consisting of >204 million substances. Our analysis of >3.2 million substances sheds light on interesting trends – namely that protein/peptide sequences appear to be of greater commercial importance than small molecules as evidenced by the substantially higher proportion in patent publications. However, a more nuanced look at the protein/peptide sequence to small molecule ratio led to insights about substances classes currently being explored with respect to emerging targets. In addition, co-occurrences between selected emerging therapies and types of cancer display interesting overlaps indicating the use of targets across various cancer types.

Given the wealth of information, systematic analysis allows for maximized learning from previously published data and discovery of hidden connections between various concepts and

ideas. Gaining nuanced insights, establishing obscure connections, and identifying concepts in their early emergent phases are bound to aid in directing research efforts in specific directions. Furthermore, timely updates to trend landscape analyses can help track the emergence of identified concepts and allow for systematic updates of emerging ideas. We hope that the insights we gleaned from our NLP-based analysis will serve as a tool which can be utilized to guide further exploration of research in immuno-oncology field.

References

1 *Cancer*, <https://www.who.int/news-room/fact-sheets/detail/cancer> (

2 Chen, S. *et al.* Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050. *JAMA Oncol* **9**, 465-472, doi:10.1001/jamaoncol.2022.7826 (2023).

3 Siegel, R. L., Miller, K. D., Wagle, N. S. & Jemal, A. Cancer statistics, 2023. *CA Cancer J Clin* **73**, 17-48, doi:10.3322/caac.21763 (2023).

4 Robert, C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* **11**, 3801, doi:10.1038/s41467-020-17670-y (2020).

5 Poole, R. M. Pembrolizumab: first global approval. *Drugs* **74**, 1973-1981, doi:10.1007/s40265-014-0314-5 (2014).

6 Beaver, J. A. *et al.* FDA Approval of Nivolumab for the First-Line Treatment of Patients with BRAF(V600) Wild-Type Unresectable or Metastatic Melanoma. *Clin Cancer Res* **23**, 3479-3483, doi:10.1158/1078-0432.CCR-16-0714 (2017).

7 Hamid, O. *et al.* Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* **30**, 582-588, doi:10.1093/annonc/mdz011 (2019).

8 Larkin, J. *et al.* Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* **381**, 1535-1546, doi:10.1056/NEJMoa1910836 (2019).

9 Garon, E. B. *et al.* Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* **372**, 2018-2028, doi:10.1056/NEJMoa1501824 (2015).

10 *FDA approves ado-trastuzumab emtansine for early breast cancer*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ado-trastuzumab-emtansine-early-breast-cancer#:~:text=On%20May%203%2C%202019%2C%20the,taxane%20and%20trastuzumab%2Dbased%20treatment.> (

11 *FDA approves inotuzumab ozogamicin for relapsed or refractory B-cell precursor ALL*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inotuzumab-ozogamicin-relapsed-or-refractory-b-cell-precursor-all#:~:text=On%20Aug.,acute%20lymphoblastic%20leukemia%20(ALL).> (

12 *FDA grants accelerated approval to mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mirvetuximab-soravtansine-gynx-fra-positive-platinum-resistant> (

13 Guerin, M., Sabatier, R. & Goncalves, A. [Trastuzumab emtansine (Kadcyla((R))) approval in HER2-positive metastatic breast cancers]. *Bull Cancer* **102**, 390-397, doi:10.1016/j.bulcan.2015.02.007 (2015).

14 Al-Salama, Z. T. Inotuzumab Ozogamicin: A Review in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia. *Target Oncol* **13**, 525-532, doi:10.1007/s11523-018-0584-z (2018).

15 *A Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers With High Folate Receptor-Alpha Expression (MIRASOL)*, <https://classic.clinicaltrials.gov/ct2/show/NCT04209855> (

16 Sasso, J. M. *et al.* The Evolving Landscape of Antibody-Drug Conjugates: In Depth Analysis of Recent Research Progress. *Bioconjug Chem*, doi:10.1021/acs.bioconjchem.3c00374 (2023).

17 *Novel Drug Approvals for 2023*, <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023> (

18 *FDA approves toripalimab-tpzi for nasopharyngeal carcinoma*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-toripalimab-tpzi-nasopharyngeal-carcinoma#:~:text=On%20October%2027%2C%202023%2C%20the,advanced%20nasopharyngeal%20carcinoma%20(NPC).> (

19 *FDA grants accelerated approval to retifanlimab-dlwr for metastatic or recurrent locally advanced Merkel cell carcinoma*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-retifanlimab-dlwr-metastatic-or-recurrent-locally-advanced-

merkel#:~:text=On%20March%2022%2C%202023%2C%20the,full%20prescribing%20information%20for%20Zynyz.> (
20 *FDA grants accelerated approval to glofitamab-gxbm for selected relapsed or refractory large B-cell lymphomas*, <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-glofitamab-gxbm-selected-relapsed-or-refractory-large-b-cell> (
21 *FDA grants accelerated approval to elranatamab-bcmm for multiple myeloma*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-elranatamab-bcmm-multiple-myeloma> (
22 *PitchBook*, <https://www.pitchbook.com/> (
23 Ivanov, J. *et al. Emerging topics – bibliometric-based methodology* (2023).
24 Jiang, Y. *et al.* Gasdermin D restricts anti-tumor immunity during PD-L1 checkpoint blockade. *Cell Rep* **41**, 111553, doi:10.1016/j.celrep.2022.111553 (2022).
25 Ager, C. R. *et al.* High potency STING agonists engage unique myeloid pathways to reverse pancreatic cancer immune privilege. *J Immunother Cancer* **9**, doi:10.1136/jitc-2021-003246 (2021).
26 Wu, F. *et al.* Inhibition of CDC20 potentiates anti-tumor immunity through facilitating GSDME-mediated pyroptosis in prostate cancer. *Exp Hematol Oncol* **12**, 67, doi:10.1186/s40164-023-00428-9 (2023).
27 Sakach, E., Sacks, R. & Kalinsky, K. Trop-2 as a Therapeutic Target in Breast Cancer. *Cancers (Basel)* **14**, doi:10.3390/cancers14235936 (2022).
28 Liu, X. *et al.* Inhibition of PCSK9 potentiates immune checkpoint therapy for cancer. *Nature* **588**, 693-698, doi:10.1038/s41586-020-2911-7 (2020).
29 Zeller, T. *et al.* Dual checkpoint blockade of CD47 and LILRB1 enhances CD20 antibody-dependent phagocytosis of lymphoma cells by macrophages. *Front Immunol* **13**, 929339, doi:10.3389/fimmu.2022.929339 (2022).
30 Upadhyaya, P. *et al.* Discovery and Optimization of a Synthetic Class of Nectin-4-Targeted CD137 Agonists for Immuno-oncology. *J Med Chem* **65**, 9858-9872, doi:10.1021/acs.jmedchem.2c00505 (2022).
31 Ray, A., Song, Y., Du, T., Chauhan, D. & Anderson, K. C. Preclinical validation of Alpha-Enolase (ENO1) as a novel immunometabolic target in multiple myeloma. *Oncogene* **39**, 2786-2796, doi:10.1038/s41388-020-1172-0 (2020).
32 Si, J. *et al.* Hematopoietic Progenitor Kinase1 (HPK1) Mediates T Cell Dysfunction and Is a Druggable Target for T Cell-Based Immunotherapies. *Cancer Cell* **38**, 551-566 e511, doi:10.1016/j.ccell.2020.08.001 (2020).
33 Cattaruzza, F. *et al.* Precision-activated T-cell engagers targeting HER2 or EGFR and CD3 mitigate on-target, off-tumor toxicity for immunotherapy in solid tumors. *Nat Cancer* **4**, 485-501, doi:10.1038/s43018-023-00536-9 (2023).
34 Pahlavanneshan, S., Sayadmanesh, A., Ebrahimiyan, H. & Basiri, M. Toll-Like Receptor-Based Strategies for Cancer Immunotherapy. *J Immunol Res* **2021**, 9912188, doi:10.1155/2021/9912188 (2021).
35 Deng, L. *et al.* Inhibition of mTOR complex 1/p70 S6 kinase signaling elevates PD-L1 levels in human cancer cells through enhancing protein stabilization accompanied with enhanced beta-TrCP degradation. *Oncogene* **38**, 6270-6282, doi:10.1038/s41388-019-0877-4 (2019).
36 Pu, D. *et al.* Cyclooxygenase-2 Inhibitor: A Potential Combination Strategy With Immunotherapy in Cancer. *Front Oncol* **11**, 637504, doi:10.3389/fonc.2021.637504 (2021).
37 Solomon, B. L. & Garrido-Laguna, I. TIGIT: a novel immunotherapy target moving from bench to bedside. *Cancer Immunol Immunother* **67**, 1659-1667, doi:10.1007/s00262-018-2246-5 (2018).
38 Shenderov, E. *et al.* Neoadjuvant enoblituzumab in localized prostate cancer: a single-arm, phase 2 trial. *Nat Med* **29**, 888-897, doi:10.1038/s41591-023-02284-w (2023).
39 Makuku, R., Khalili, N., Razi, S., Keshavarz-Fathi, M. & Rezaei, N. Current and Future Perspectives of PD-1/PDL-1 Blockade in Cancer Immunotherapy. *J Immunol Res* **2021**, 6661406, doi:10.1155/2021/6661406 (2021).
40 Opitz, C. A. *et al.* The therapeutic potential of targeting tryptophan catabolism in cancer. *Br J Cancer* **122**, 30-44, doi:10.1038/s41416-019-0664-6 (2020).

41 Jiang, Y. *et al.* TANK-Binding Kinase 1 (TBK1) Serves as a Potential Target for Hepatocellular Carcinoma by Enhancing Tumor Immune Infiltration. *Front Immunol* **12**, 612139, doi:10.3389/fimmu.2021.612139 (2021).
42 Chen, H. *et al.* Ruxolitinib reverses checkpoint inhibition by reducing programmed cell death ligand-1 (PD-L1) expression and increases anti-tumour effects of T cells in multiple myeloma. *Br J Haematol* **192**, 568-576, doi:10.1111/bjh.17282 (2021).
43 Zahra, K., Dey, T., Ashish, Mishra, S. P. & Pandey, U. Pyruvate Kinase M2 and Cancer: The Role of PKM2 in Promoting Tumorigenesis. *Front Oncol* **10**, 159, doi:10.3389/fonc.2020.00159 (2020).
44 Yang, Y. *et al.* Emerging Sonodynamic Therapy-Based Nanomedicines for Cancer Immunotherapy. *Adv Sci (Weinh)* **10**, e2204365, doi:10.1002/advs.202204365 (2023).
45 Wang, M. *et al.* Tumor-Microenvironment-Activated Reactive Oxygen Species Amplifier for Enzymatic Cascade Cancer Starvation/Chemodynamic /Immunotherapy. *Adv Mater* **34**, e2106010, doi:10.1002/adma.202106010 (2022).
46 Singh, A. K. & McGuirk, J. P. CAR T cells: continuation in a revolution of immunotherapy. *Lancet Oncol* **21**, e168-e178, doi:10.1016/S1470-2045(19)30823-X (2020).
47 Meng, Z., Zhang, Y., Zhou, X., Ji, J. & Liu, Z. Nanovaccines with cell-derived components for cancer immunotherapy. *Adv Drug Deliv Rev* **182**, 114107, doi:10.1016/j.addr.2021.114107 (2022).
48 Zhu, Q. *et al.* Hematopoietic Progenitor Kinase 1 in Tumor Immunology: A Medicinal Chemistry Perspective. *J Med Chem* **65**, 8065-8090, doi:10.1021/acs.jmedchem.2c00172 (2022).
49 Niswander, L. M. *et al.* Potent preclinical activity of FLT3-directed chimeric antigen receptor T-cell immunotherapy against FLT3- mutant acute myeloid leukemia and KMT2A-rearranged acute lymphoblastic leukemia. *Haematologica* **108**, 457-471, doi:10.3324/haematol.2022.281456 (2023).
50 Nur Husna, S. M. & Wong, K. K. Margetuximab and trastuzumab deruxtecan: New generation of anti-HER2 immunotherapeutic agents for breast cancer. *Mol Immunol* **152**, 45-54, doi:10.1016/j.molimm.2022.10.005 (2022).
51 Gardner, A., de Mingo Pulido, A. & Ruffell, B. Dendritic Cells and Their Role in Immunotherapy. *Front Immunol* **11**, 924, doi:10.3389/fimmu.2020.00924 (2020).
52 Borcoman, E. *et al.* HDAC Inhibition to Prime Immune Checkpoint Inhibitors. *Cancers (Basel)* **14**, doi:10.3390/cancers14010066 (2021).
53 Zhang, Z. & Richmond, A. The Role of PI3K Inhibition in the Treatment of Breast Cancer, Alone or Combined With Immune Checkpoint Inhibitors. *Front Mol Biosci* **8**, 648663, doi:10.3389/fmolb.2021.648663 (2021).
54 Zeindler, J. *et al.* Nectin-4 Expression Is an Independent Prognostic Biomarker and Associated With Better Survival in Triple-Negative Breast Cancer. *Front Med (Lausanne)* **6**, 200, doi:10.3389/fmed.2019.00200 (2019).
55 Lu, M. *et al.* Pan-cancer analysis of SETD2 mutation and its association with the efficacy of immunotherapy. *NPJ Precis Oncol* **5**, 51, doi:10.1038/s41698-021-00193-0 (2021).
56 Huang, C. K., Sun, Y., Lv, L. & Ping, Y. ENO1 and Cancer. *Mol Ther Oncolytics* **24**, 288-298, doi:10.1016/j.omto.2021.12.026 (2022).
57 Shvartsur, A. & Bonavida, B. Trop2 and its overexpression in cancers: regulation and clinical/therapeutic implications. *Genes Cancer* **6**, 84-105, doi:10.18632/genesandcancer.40 (2015).
58 Chan, T. A. *et al.* Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol* **30**, 44-56, doi:10.1093/annonc/mdy495 (2019).
59 Sun, C. *et al.* Identification and validation of PCSK9 as a prognostic and immune-related influencing factor in tumorigenesis: a pan-cancer analysis. *Front Oncol* **13**, 1134063, doi:10.3389/fonc.2023.1134063 (2023).
60 Cheng, J. *et al.* Leukocyte immunoglobulin-like receptor subfamily B member 1 potentially acts as a diagnostic and prognostic target in certain subtypes of adenocarcinoma. *Med Hypotheses* **144**, 109863, doi:10.1016/j.mehy.2020.109863 (2020).
61 Philipson, E., Engstrom, C., Naredi, P. & Bourghardt Fagman, J. High expression of p62/SQSTM1 predicts shorter survival for patients with pancreatic cancer. *BMC Cancer* **22**, 347, doi:10.1186/s12885-022-09468-6 (2022).
62 Tudor, D. V. *et al.* COX-2 as a potential biomarker and therapeutic target in melanoma. *Cancer Biol Med* **17**, 20-31, doi:10.20892/j.issn.2095-3941.2019.0339 (2020).

63 Hu, Y., Liu, Z. & Tang, H. Tryptophan 2,3-dioxygenase may be a potential prognostic biomarker and immunotherapy target in cancer: A meta-analysis and bioinformatics analysis. *Front Oncol* **12**, 977640, doi:10.3389/fonc.2022.977640 (2022).
64 Woo, S. R. *et al.* Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* **72**, 917-927, doi:10.1158/0008-5472.CAN-11-1620 (2012).
65 Leone, R. D., Lo, Y. C. & Powell, J. D. A2aR antagonists: Next generation checkpoint blockade for cancer immunotherapy. *Comput Struct Biotechnol J* **13**, 265-272, doi:10.1016/j.csbj.2015.03.008 (2015).
66 Johnston, R. J., Yu, X. & Grogan, J. L. The checkpoint inhibitor TIGIT limits antitumor and antiviral CD8(+) T cell responses. *Oncoimmunology* **4**, e1036214, doi:10.1080/2162402X.2015.1036214 (2015).
67 Fu, T., He, Q. & Sharma, P. The ICOS/ICOSL pathway is required for optimal antitumor responses mediated by anti-CTLA-4 therapy. *Cancer Res* **71**, 5445-5454, doi:10.1158/0008-5472.CAN-11-1138 (2011).
68 He, J., Hu, Y., Hu, M. & Li, B. Development of PD-1/PD-L1 Pathway in Tumor Immune Microenvironment and Treatment for Non-Small Cell Lung Cancer. *Sci Rep* **5**, 13110, doi:10.1038/srep13110 (2015).
69 Zimmermann, S., Peters, S., Owinokoko, T. & Gadgeel, S. M. Immune Checkpoint Inhibitors in the Management of Lung Cancer. *Am Soc Clin Oncol Educ Book* **38**, 682-695, doi:10.1200/EDBK_201319 (2018).
70 Xia, L., Liu, Y. & Wang, Y. PD-1/PD-L1 Blockade Therapy in Advanced Non-Small-Cell Lung Cancer: Current Status and Future Directions. *Oncologist* **24**, S31-S41, doi:10.1634/theoncologist.2019-IO-S1-s05 (2019).
71 Barok, M., Joensuu, H. & Isola, J. Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Res* **16**, 209, doi:10.1186/bcr3621 (2014).
72 Modi, S. *et al.* Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* **382**, 610-621, doi:10.1056/NEJMoa1914510 (2020).
73 Bardia, A. *et al.* Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med* **384**, 1529-1541, doi:10.1056/NEJMoa2028485 (2021).
74 Coleman, N., Yap, T. A., Heymach, J. V., Meric-Bernstam, F. & Le, X. Antibody-drug conjugates in lung cancer: dawn of a new era? *NPJ Precis Oncol* **7**, 5, doi:10.1038/s41698-022-00338-9 (2023).
75 *FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung> (
76 Ranoa, D. R. E. *et al.* Single CAR-T cell treatment controls disseminated ovarian cancer in a syngeneic mouse model. *J Immunother Cancer* **11**, doi:10.1136/jitc-2022-006509 (2023).
77 Yan, W., Hu, H. & Tang, B. Advances Of Chimeric Antigen Receptor T Cell Therapy In Ovarian Cancer. *Onco Targets Ther* **12**, 8015-8022, doi:10.2147/OTT.S203550 (2019).
78 *CAS Registry*, <https://www.cas.org/cas-data/cas-registry> (
79 *Pharmaprojects*, <https://www.citeline.com/en/products-services/clinical/pharmaprojects> (
80 Vinay, D. S. *et al.* Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol* **35 Suppl**, S185-S198, doi:10.1016/j.semcancer.2015.03.004 (2015).
81 *FDA D.I.S.C.O.: Burst Edition: FDA approvals of Opdualag (nivolumab and relatlimab-rmbw) for unresectable or metastatic melanoma, and Keytruda (pembrolizumab) for patients with advanced endometrial carcinoma*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approvals-opdualag-nivolumab-and-relatlimab-rmbw-unresectable-or#:~:text=On%20March%2018%2C%202022%2C%20the,with%20unresectable%20or%20metastatic%20melanoma.> (
82 Chin, S. M. *et al.* Structure of the 4-1BB/4-1BBL complex and distinct binding and functional properties of utomilumab and urelumab. *Nat Commun* **9**, 4679, doi:10.1038/s41467-018-07136-7 (2018).

83 Dwivedi, S., Rendon-Huerta, E. P., Ortiz-Navarrete, V. & Montano, L. F. CD38 and Regulation of the Immune Response Cells in Cancer. *J Oncol* **2021**, 6630295, doi:10.1155/2021/6630295 (2021).
84 *Darzalex*, <https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761036s041lbl.pdf> (
85 *Daratumumab (DARZALEX)*, <https://www.fda.gov/drugs/resources-information-approved-drugs/daratumumab-darzalex> (
86 Nijhof, I. S. *et al.* Upregulation of CD38 expression on multiple myeloma cells by all-trans retinoic acid improves the efficacy of daratumumab. *Leukemia* **29**, 2039-2049, doi:10.1038/leu.2015.123 (2015).
87 de Weers, M. *et al.* Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* **186**, 1840-1848, doi:10.4049/jimmunol.1003032 (2011).
88 Zhang, C., Liu, J., Zhong, J. F. & Zhang, X. Engineering CAR-T cells. *Biomark Res* **5**, 22, doi:10.1186/s40364-017-0102-y (2017).
89 Wu, L., Wei, Q., Brzostek, J. & Gascoigne, N. R. J. Signaling from T cell receptors (TCRs) and chimeric antigen receptors (CARs) on T cells. *Cell Mol Immunol* **17**, 600-612, doi:10.1038/s41423-020-0470-3 (2020).
90 Maude, S. L. *et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* **371**, 1507-1517, doi:10.1056/NEJMoa1407222 (2014).
91 Garfall, A. L. *et al.* Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. *N Engl J Med* **373**, 1040-1047, doi:10.1056/NEJMoa1504542 (2015).
92 Ali, S. A. *et al.* T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood* **128**, 1688-1700, doi:10.1182/blood-2016-04-711903 (2016).
93 Le, R. Q. *et al.* FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist* **23**, 943-947, doi:10.1634/theoncologist.2018-0028 (2018).
94 Zhang, X., Zhu, L., Zhang, H., Chen, S. & Xiao, Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. *Front Immunol* **13**, 927153, doi:10.3389/fimmu.2022.927153 (2022).
95 Jiang, H. *et al.* Claudin18.2-Specific Chimeric Antigen Receptor Engineered T Cells for the Treatment of Gastric Cancer. *J Natl Cancer Inst* **111**, 409-418, doi:10.1093/jnci/djy134 (2019).
96 Batra, S. A. *et al.* Glypican-3-Specific CAR T Cells Coexpressing IL15 and IL21 Have Superior Expansion and Antitumor Activity against Hepatocellular Carcinoma. *Cancer Immunol Res* **8**, 309-320, doi:10.1158/2326-6066.CIR-19-0293 (2020).
97 Hu, Z. *et al.* LunX-CAR T Cells as a Targeted Therapy for Non-Small Cell Lung Cancer. *Mol Ther Oncolytics* **17**, 361-370, doi:10.1016/j.omto.2020.04.008 (2020).
98 Zhang, K. *et al.* Bright future or blind alley? CAR-T cell therapy for solid tumors. *Front Immunol* **14**, 1045024, doi:10.3389/fimmu.2023.1045024 (2023).
99 *CAR-T*, <https://classic.clinicaltrials.gov/ct2/results?cond=CAR-T&term=&cntry=&state=&city=&dist=> (
100 Wang, V., Gauthier, M., Decot, V., Reppel, L. & Bensoussan, D. Systematic Review on CAR-T Cell Clinical Trials Up to 2022: Academic Center Input. *Cancers (Basel)* **15**, doi:10.3390/cancers15041003 (2023).
101 *CAR | Solid Tumor*, <https://classic.clinicaltrials.gov/ct2/results?cond=Solid+Tumor&term=CAR&cntry=&state=&city=&dist=> (
102 Maalej, K. M. *et al.* CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances. *Mol Cancer* **22**, 20, doi:10.1186/s12943-023-01723-z (2023).
103 Yang, J., Chen, Y., Jing, Y., Green, M. R. & Han, L. Advancing CAR T cell therapy through the use of multidimensional omics data. *Nat Rev Clin Oncol* **20**, 211-228, doi:10.1038/s41571-023-00729-2 (2023).
104 Chen, Z., Hu, Y. & Mei, H. Advances in CAR-Engineered Immune Cell Generation: Engineering Approaches and Sourcing Strategies. *Adv Sci (Weinh)*, e2303215, doi:10.1002/advs.202303215 (2023).

105 Schwartz, R. S. Paul Ehrlich's magic bullets. *N Engl J Med* **350**, 1079-1080, doi:10.1056/NEJMp048021 (2004).
106 Qian, L. *et al.* The Dawn of a New Era: Targeting the "Undruggables" with Antibody-Based Therapeutics. *Chem Rev* **123**, 7782-7853, doi:10.1021/acs.chemrev.2c00915 (2023).
107 Fuentes-Antras, J., Genta, S., Vijenthira, A. & Siu, L. L. Antibody-drug conjugates: in search of partners of choice. *Trends Cancer* **9**, 339-354, doi:10.1016/j.trecan.2023.01.003 (2023).
108 Tapia-Galisteo, A., Compte, M., Alvarez-Vallina, L. & Sanz, L. When three is not a crowd: trispecific antibodies for enhanced cancer immunotherapy. *Theranostics* **13**, 1028-1041, doi:10.7150/thno.81494 (2023).
109 Ziaei, V. *et al.* Production and characterization of a camelid single domain anti-CD22 antibody conjugated to DM1. *Mol Cell Biochem*, doi:10.1007/s11010-023-04741-z (2023).
110 Sheyi, R., de la Torre, B. G. & Albericio, F. Linkers: An Assurance for Controlled Delivery of Antibody-Drug Conjugate. *Pharmaceutics* **14**, doi:10.3390/pharmaceutics14020396 (2022).
111 Baah, S., Laws, M. & Rahman, K. M. Antibody-Drug Conjugates-A Tutorial Review. *Molecules* **26**, doi:10.3390/molecules26102943 (2021).
112 Zhang, D. *et al.* Exposure-Efficacy Analysis of Antibody-Drug Conjugates Delivering an Excessive Level of Payload to Tissues. *Drug Metab Dispos* **47**, 1146-1155, doi:10.1124/dmd.119.087023 (2019).
113 Dumontet, C., Reichert, J. M., Senter, P. D., Lambert, J. M. & Beck, A. Antibody-drug conjugates come of age in oncology. *Nat Rev Drug Discov* **22**, 641-661, doi:10.1038/s41573-023-00709-2 (2023).
114 Lin, M. J. *et al.* Cancer vaccines: the next immunotherapy frontier. *Nat Cancer* **3**, 911-926, doi:10.1038/s43018-022-00418-6 (2022).
115 Smith, C. C. *et al.* Alternative tumour-specific antigens. *Nat Rev Cancer* **19**, 465-478, doi:10.1038/s41568-019-0162-4 (2019).
116 Li, L., Goedegebuure, S. P. & Gillanders, W. Cancer vaccines: shared tumor antigens return to the spotlight. *Signal Transduct Target Ther* **5**, 251, doi:10.1038/s41392-020-00364-8 (2020).
117 *Cervarix*, <https://www.fda.gov/media/78013/download> (
118 *Gardasil-9*, <https://www.fda.gov/media/90064/download?attachment> (
119 *Heplisav-B*, <https://www.fda.gov/media/108745/download> (
120 Lobo, N. *et al.* 100 years of Bacillus Calmette-Guerin immunotherapy: from cattle to COVID-19. *Nat Rev Urol* **18**, 611-622, doi:10.1038/s41585-021-00481-1 (2021).
121 *Provenge*, <https://www.fda.gov/media/78511/download> (
122 Liu, W. *et al.* Peptide-based therapeutic cancer vaccine: Current trends in clinical application. *Cell Prolif* **54**, e13025, doi:10.1111/cpr.13025 (2021).
123 Perez-Banos, A. *et al.* Whole tumour cell-based vaccines: tuning the instruments to orchestrate an optimal antitumour immune response. *Br J Cancer* **129**, 572-585, doi:10.1038/s41416-023-02327-6 (2023).
124 Meng, J. *et al.* Generation of whole tumor cell vaccine for on-demand manipulation of immune responses against cancer under near-infrared laser irradiation. *Nat Commun* **14**, 4505, doi:10.1038/s41467-023-40207-y (2023).
125 Cheever, M. A. & Higano, C. S. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin Cancer Res* **17**, 3520-3526, doi:10.1158/1078-0432.CCR-10-3126 (2011).
126 Rahman, M. M. & McFadden, G. Oncolytic Viruses: Newest Frontier for Cancer Immunotherapy. *Cancers (Basel)* **13**, doi:10.3390/cancers13215452 (2021).
127 Ma, R., Li, Z., Chiocca, E. A., Caligiuri, M. A. & Yu, J. The emerging field of oncolytic virus-based cancer immunotherapy. *Trends Cancer* **9**, 122-139, doi:10.1016/j.trecan.2022.10.003 (2023).
128 *Adstiladrin*, <https://www.fda.gov/media/164029/download> (
129 *FDA D.I.S.C.O. Burst Edition: FDA approval of Adstiladrin (nadofaragene firadenovec-vncg) for patients with high-risk Bacillus Calmette-Guérin unresponsive non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors*, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-adstiladrin-nadofaragene-firadenovec-vncg-patients-high-risk> (
130 *Imlygic*, <https://www.fda.gov/media/94129/download> (

131 Miao, L., Zhang, Y. & Huang, L. mRNA vaccine for cancer immunotherapy. *Mol Cancer* **20**, 41, doi:10.1186/s12943-021-01335-5 (2021).
132 Lorentzen, C. L., Haanen, J. B., Met, O. & Svane, I. M. Clinical advances and ongoing trials on mRNA vaccines for cancer treatment. *Lancet Oncol* **23**, e450-e458, doi:10.1016/S1470-2045(22)00372-2 (2022).
133 Fang, X., Lan, H., Jin, K., Gong, D. & Qian, J. Nanovaccines for Cancer Prevention and Immunotherapy: An Update Review. *Cancers (Basel)* **14**, doi:10.3390/cancers14163842 (2022).
134 Liu, S. *et al.* NK cell-based cancer immunotherapy: from basic biology to clinical development. *J Hematol Oncol* **14**, 7, doi:10.1186/s13045-020-01014-w (2021).
135 Sakamoto, N. *et al.* Phase I clinical trial of autologous NK cell therapy using novel expansion method in patients with advanced digestive cancer. *J Transl Med* **13**, 277, doi:10.1186/s12967-015-0632-8 (2015).
136 Miller, J. S. *et al.* Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood* **105**, 3051-3057, doi:10.1182/blood-2004-07-2974 (2005).
137 Rosenberg, S. A. *et al.* Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* **313**, 1485-1492, doi:10.1056/NEJM198512053132327 (1985).
138 Ruggeri, L. *et al.* Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* **295**, 2097-2100, doi:10.1126/science.1068440 (2002).
139 Ishikawa, E. *et al.* Autologous natural killer cell therapy for human recurrent malignant glioma. *Anticancer Res* **24**, 1861-1871 (2004).
140 Shah, N. N. *et al.* Acute GVHD in patients receiving IL-15/4-1BBL activated NK cells following T-cell-depleted stem cell transplantation. *Blood* **125**, 784-792, doi:10.1182/blood-2014-07-592881 (2015).
141 Romee, R. *et al.* Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci Transl Med* **8**, 357ra123, doi:10.1126/scitranslmed.aaf2341 (2016).
142 Hermanson, D. L. & Kaufman, D. S. Utilizing chimeric antigen receptors to direct natural killer cell activity. *Front Immunol* **6**, 195, doi:10.3389/fimmu.2015.00195 (2015).
143 Liu, E. *et al.* Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. *N Engl J Med* **382**, 545-553, doi:10.1056/NEJMoa1910607 (2020).
144 Cichocki, F. *et al.* GSK3 Inhibition Drives Maturation of NK Cells and Enhances Their Antitumor Activity. *Cancer Res* **77**, 5664-5675, doi:10.1158/0008-5472.CAN-17-0799 (2017).
145 Du, N., Guo, F., Wang, Y. & Cui, J. NK Cell Therapy: A Rising Star in Cancer Treatment. *Cancers (Basel)* **13**, doi:10.3390/cancers13164129 (2021).
146 Kaulfuss, M. *et al.* The NK cell checkpoint NKG2A maintains expansion capacity of human NK cells. *Sci Rep* **13**, 10555, doi:10.1038/s41598-023-37779-6 (2023).
147 Yang, Q. *et al.* The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy. *Acta Pharm Sin B* **10**, 2156-2170, doi:10.1016/j.apsb.2020.04.004 (2020).
148 Zhou, J. *et al.* Tumor-Associated Macrophages: Recent Insights and Therapies. *Front Oncol* **10**, 188, doi:10.3389/fonc.2020.00188 (2020).
149 *CAR-macrophages for the Treatment of HER2 Overexpressing Solid Tumors*, <https://www.clinicaltrials.gov/study/NCT04660929> (
150 Su, M. J., Aldawsari, H. & Amiji, M. Pancreatic Cancer Cell Exosome-Mediated Macrophage Reprogramming and the Role of MicroRNAs 155 and 125b2 Transfection using Nanoparticle Delivery Systems. *Sci Rep* **6**, 30110, doi:10.1038/srep30110 (2016).
151 Parayath, N. N., Parikh, A. & Amiji, M. M. Repolarization of Tumor-Associated Macrophages in a Genetically Engineered Nonsmall Cell Lung Cancer Model by Intraperitoneal Administration of Hyaluronic Acid-Based Nanoparticles Encapsulating MicroRNA-125b. *Nano Lett* **18**, 3571-3579, doi:10.1021/acs.nanolett.8b00689 (2018).
152 Ortega, R. A. *et al.* Manipulating the NF-kappaB pathway in macrophages using mannosylated, siRNA-delivering nanoparticles can induce immunostimulatory and tumor cytotoxic functions. *Int J Nanomedicine* **11**, 2163-2177, doi:10.2147/IJN.S93483 (2016).
153 van Dalen, F. J., van Stevendaal, M., Fennemann, F. L., Verdoes, M. & Ilina, O. Molecular Repolarisation of Tumour-Associated Macrophages. *Molecules* **24**, doi:10.3390/molecules24010009 (2018).

154 Li, Z. *et al.* Depletion of tumor associated macrophages enhances local and systemic platelet-mediated anti-PD-1 delivery for post-surgery tumor recurrence treatment. *Nat Commun* **13**, 1845, doi:10.1038/s41467-022-29388-0 (2022).
155 Gobel, A. *et al.* Anti-tumor effects of mevalonate pathway inhibition in ovarian cancer. *BMC Cancer* **20**, 703, doi:10.1186/s12885-020-07164-x (2020).
156 Fujiwara, T. *et al.* CSF1/CSF1R Signaling Inhibitor Pexidartinib (PLX3397) Reprograms Tumor-Associated Macrophages and Stimulates T-cell Infiltration in the Sarcoma Microenvironment. *Mol Cancer Ther* **20**, 1388-1399, doi:10.1158/1535-7163.MCT-20-0591 (2021).
157 Yang, M. *et al.* Cancer Immunotherapy and Delivery System: An Update. *Pharmaceutics* **14**, doi:10.3390/pharmaceutics14081630 (2022).
158 Yong, T., Wei, Z., Gan, L. & Yang, X. Extracellular-Vesicle-Based Drug Delivery Systems for Enhanced Antitumor Therapies through Modulating the Cancer-Immunity Cycle. *Adv Mater* **34**, e2201054, doi:10.1002/adma.202201054 (2022).
159 Zhu, S. *et al.* Combination strategies to maximize the benefits of cancer immunotherapy. *J Hematol Oncol* **14**, 156, doi:10.1186/s13045-021-01164-5 (2021).
160 Riley, R. S., June, C. H., Langer, R. & Mitchell, M. J. Delivery technologies for cancer immunotherapy. *Nat Rev Drug Discov* **18**, 175-196, doi:10.1038/s41573-018-0006-z (2019).
161 Shi, J., Kantoff, P. W., Wooster, R. & Farokhzad, O. C. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer* **17**, 20-37, doi:10.1038/nrc.2016.108 (2017).
162 Gao, S. *et al.* Engineering Nanoparticles for Targeted Remodeling of the Tumor Microenvironment to Improve Cancer Immunotherapy. *Theranostics* **9**, 126-151, doi:10.7150/thno.29431 (2019).
163 Saeed, M., Gao, J., Shi, Y., Lammers, T. & Yu, H. Engineering Nanoparticles to Reprogram the Tumor Immune Microenvironment for Improved Cancer Immunotherapy. *Theranostics* **9**, 7981-8000, doi:10.7150/thno.37568 (2019).
164 Bertrand, N., Wu, J., Xu, X., Kamaly, N. & Farokhzad, O. C. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv Drug Deliv Rev* **66**, 2-25, doi:10.1016/j.addr.2013.11.009 (2014).
165 *Doxil*, <https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf> (
166 Barenholz, Y. Doxil(R)--the first FDA-approved nano-drug: lessons learned. *J Control Release* **160**, 117-134, doi:10.1016/j.jconrel.2012.03.020 (2012).
167 *Abraxane*, <https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021660s047lbl.pdf> (
168 Green, M. R. *et al.* Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* **17**, 1263-1268, doi:10.1093/annonc/mdl104 (2006).
169 Hao, Y. *et al.* Lipid-based nanoparticles as drug delivery systems for cancer immunotherapy. *MedComm (2020)* **4**, e339, doi:10.1002/mco2.339 (2023).
170 Tenchov, R., Bird, R., Curtze, A. E. & Zhou, Q. Lipid Nanoparticles horizontal line From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. *ACS Nano* **15**, 16982-17015, doi:10.1021/acsnano.1c04996 (2021).
171 Anselmo, A. C. & Mitragotri, S. Nanoparticles in the clinic: An update. *Bioeng Transl Med* **4**, e10143, doi:10.1002/btm2.10143 (2019).
172 Harris, J. M., Martin, N. E. & Modi, M. Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* **40**, 539-551, doi:10.2165/00003088-200140070-00005 (2001).
173 Tenchov, R., Sasso, J. M. & Zhou, Q. A. PEGylated Lipid Nanoparticle Formulations: Immunological Safety and Efficiency Perspective. *Bioconjug Chem* **34**, 941-960, doi:10.1021/acs.bioconjchem.3c00174 (2023).
174 Felgner, P. L. *et al.* Lipofection: a highly efficient, lipid-mediated DNA-transfection procedure. *Proc Natl Acad Sci U S A* **84**, 7413-7417, doi:10.1073/pnas.84.21.7413 (1987).
175 Muller, R. H., Mader, K. & Gohla, S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. *Eur J Pharm Biopharm* **50**, 161-177, doi:10.1016/s0939-6411(00)00087-4 (2000).
176 Semple, S. C. *et al.* Rational design of cationic lipids for siRNA delivery. *Nat Biotechnol* **28**, 172-176, doi:10.1038/nbt.1602 (2010).
177 Evans, E. R., Bugga, P., Asthana, V. & Drezek, R. Metallic Nanoparticles for Cancer Immunotherapy. *Mater Today (Kidlington)* **21**, 673-685, doi:10.1016/j.mattod.2017.11.022 (2018).

178 Medarova, Z., Pham, W., Farrar, C., Petkova, V. & Moore, A. In vivo imaging of siRNA delivery and silencing in tumors. *Nat Med* **13**, 372-377, doi:10.1038/nm1486 (2007).
179 Yamada, M., Foote, M. & Prow, T. W. Therapeutic gold, silver, and platinum nanoparticles. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **7**, 428-445, doi:10.1002/wnan.1322 (2015).
180 Kovacs, D., Igaz, N., Gopisetty, M. K. & Kiricsi, M. Cancer Therapy by Silver Nanoparticles: Fiction or Reality? *Int J Mol Sci* **23**, doi:10.3390/ijms23020839 (2022).
181 Shipunova, V. O. *et al.* Photothermal Therapy with HER2-Targeted Silver Nanoparticles Leading to Cancer Remission. *Pharmaceutics* **14**, doi:10.3390/pharmaceutics14051013 (2022).
182 He, J. S. *et al.* The Application of and Strategy for Gold Nanoparticles in Cancer Immunotherapy. *Front Pharmacol* **12**, 687399, doi:10.3389/fphar.2021.687399 (2021).
183 Cheng, L., Wang, C., Feng, L., Yang, K. & Liu, Z. Functional nanomaterials for phototherapies of cancer. *Chem Rev* **114**, 10869-10939, doi:10.1021/cr400532z (2014).
184 Vines, J. B., Yoon, J. H., Ryu, N. E., Lim, D. J. & Park, H. Gold Nanoparticles for Photothermal Cancer Therapy. *Front Chem* **7**, 167, doi:10.3389/fchem.2019.00167 (2019).
185 Yu, A. *et al.* Recent Advances of Mesoporous Silica as a Platform for Cancer Immunotherapy. *Biosensors (Basel)* **12**, doi:10.3390/bios12020109 (2022).
186 Grun, M., Lauer, I. & Unger, K. K. The synthesis of micrometer- and submicrometer-size spheres of ordered mesoporous oxide MCM-41. *Advanced Materials* **9**, 254-257, doi:10.1002/adma.19970090317 (1997).
187 Vallet-Regi, M., Rámila, A., del Real, R. P. & Pérez-Pariente, J. A New Property of MCM-41: Drug Delivery System. *Chem. Mater.* **13**, 308-311, doi:10.1021/cm0011559 (2001).
188 Wang, X. *et al.* Comprehensive Mechanism Analysis of Mesoporous-Silica-Nanoparticle-Induced Cancer Immunotherapy. *Adv Healthc Mater* **5**, 1169-1176, doi:10.1002/adhm.201501013 (2016).
189 Wang, X. *et al.* Erratum to Supporting Information of Comprehensive Mechanism Analysis of Mesoporous-Silica-Nanoparticle-Induced Cancer Immunotherapy. *Adv Healthc Mater* **8**, e1901432, doi:10.1002/adhm.201901432 (2019).
190 Escriche-Navarro, B. *et al.* Mesoporous Silica Materials as an Emerging Tool for Cancer Immunotherapy. *Adv Sci (Weinh)* **9**, e2200756, doi:10.1002/advs.202200756 (2022).
191 Yu, Z. *et al.* Smart Polymeric Nanoparticles in Cancer Immunotherapy. *Pharmaceutics* **15**, doi:10.3390/pharmaceutics15030775 (2023).
192 Mirhadi, E. *et al.* Redox-sensitive nanoscale drug delivery systems for cancer treatment. *Int J Pharm* **589**, 119882, doi:10.1016/j.ijpharm.2020.119882 (2020).
193 Wang, L. *et al.* PEGylated reduced-graphene oxide hybridized with Fe(3)O(4) nanoparticles for cancer photothermal-immunotherapy. *J Mater Chem B* **7**, 7406-7414, doi:10.1039/c9tb00630c (2019).
194 Tenchov, R. *et al.* Exosomes horizontal line Nature's Lipid Nanoparticles, a Rising Star in Drug Delivery and Diagnostics. *ACS Nano* **16**, 17802-17846, doi:10.1021/acsnano.2c08774 (2022).
195 Zhao, Y. *et al.* Exosomes in cancer immunoediting and immunotherapy. *Asian J Pharm Sci* **17**, 193-205, doi:10.1016/j.ajps.2021.12.001 (2022).
196 Cao, Y. *et al.* Exosomes and cancer immunotherapy: A review of recent cancer research. *Front Oncol* **12**, 1118101, doi:10.3389/fonc.2022.1118101 (2022).
197 Xie, F. *et al.* Extracellular Vesicles in Cancer Immune Microenvironment and Cancer Immunotherapy. *Adv Sci (Weinh)* **6**, 1901779, doi:10.1002/advs.201901779 (2019).
198 Pitt, J. M. *et al.* Dendritic cell-derived exosomes for cancer therapy. *J Clin Invest* **126**, 1224-1232, doi:10.1172/JCI81137 (2016).
199 Yao, Y., Fu, C., Zhou, L., Mi, Q. S. & Jiang, A. DC-Derived Exosomes for Cancer Immunotherapy. *Cancers (Basel)* **13**, doi:10.3390/cancers13153667 (2021).
200 Luo, C., Sun, J., Sun, B. & He, Z. Prodrug-based nanoparticulate drug delivery strategies for cancer therapy. *Trends Pharmacol Sci* **35**, 556-566, doi:10.1016/j.tips.2014.09.008 (2014).
201 Cho, N. H. *et al.* A multifunctional core-shell nanoparticle for dendritic cell-based cancer immunotherapy. *Nat Nanotechnol* **6**, 675-682, doi:10.1038/nnano.2011.149 (2011).
202 Kovacs, D. *et al.* Core-shell nanoparticles suppress metastasis and modify the tumour-supportive activity of cancer-associated fibroblasts. *J Nanobiotechnology* **18**, 18, doi:10.1186/s12951-020-0576-x (2020).
203 Li, J. *et al.* Hybrid Nanomaterials for Cancer Immunotherapy. *Adv Sci (Weinh)* **10**, e2204932, doi:10.1002/advs.202204932 (2023).

204 Naher, H. S. *et al.* Upconversion nanoparticles (UCNPs): Synthesis methods, imaging and cancer therapy. *Journal of Drug Delivery Science and Technology* **80**, 104175, doi:10.1016/j.jddst.2023.104175 (2023).
205 Yu, H., Wu, M., Chen, S., Song, M. & Yue, Y. Biomimetic nanoparticles for tumor immunotherapy. *Front Bioeng Biotechnol* **10**, 989881, doi:10.3389/fbioe.2022.989881 (2022).
206 Zeng, Y. *et al.* Cell membrane coated-nanoparticles for cancer immunotherapy. *Acta Pharm Sin B* **12**, 3233-3254, doi:10.1016/j.apsb.2022.02.023 (2022).
207 Palange, A. L., Palomba, R., Rizzuti, I. F., Ferreira, M. & Decuzzi, P. Deformable Discoidal Polymeric Nanoconstructs for the Precise Delivery of Therapeutic and Imaging Agents. *Mol Ther* **25**, 1514-1521, doi:10.1016/j.ymthe.2017.02.012 (2017).
208 Zhou, W., Jia, Y., Liu, Y., Chen, Y. & Zhao, P. Tumor Microenvironment-Based Stimuli-Responsive Nanoparticles for Controlled Release of Drugs in Cancer Therapy. *Pharmaceutics* **14**, doi:10.3390/pharmaceutics14112346 (2022).
209 Saw, P. E. *et al.* Stimuli-Responsive Polymer-Prodrug Hybrid Nanoplatform for Multistage siRNA Delivery and Combination Cancer Therapy. *Nano Lett* **19**, 5967-5974, doi:10.1021/acs.nanolett.9b01660 (2019).
210 Bildstein, L., Dubernet, C. & Couvreur, P. Prodrug-based intracellular delivery of anticancer agents. *Adv Drug Deliv Rev* **63**, 3-23, doi:10.1016/j.addr.2010.12.005 (2011).
211 Tobore, T. O. On the need for the development of a cancer early detection, diagnostic, prognosis, and treatment response system. *Future Sci OA* **6**, FSO439, doi:10.2144/fsoa-2019-0028 (2019).
212 Tappia, P. S. & Ramjiawan, B. Biomarkers for Early Detection of Cancer: Molecular Aspects. *Int J Mol Sci* **24**, doi:10.3390/ijms24065272 (2023).
213 Almaguel, F. A., Sanchez, T. W., Ortiz-Hernandez, G. L. & Casiano, C. A. Alpha-Enolase: Emerging Tumor-Associated Antigen, Cancer Biomarker, and Oncotherapeutic Target. *Front Genet* **11**, 614726, doi:10.3389/fgene.2020.614726 (2020).
214 Tu, S. H. *et al.* Increased expression of enolase alpha in human breast cancer confers tamoxifen resistance in human breast cancer cells. *Breast Cancer Res Treat* **121**, 539-553, doi:10.1007/s10549-009-0492-0 (2010).
215 Chang, G. C. *et al.* Identification of alpha-enolase as an autoantigen in lung cancer: its overexpression is associated with clinical outcomes. *Clin Cancer Res* **12**, 5746-5754, doi:10.1158/1078-0432.CCR-06-0324 (2006).
216 Hsiao, K. C. *et al.* Surface alpha-enolase promotes extracellular matrix degradation and tumor metastasis and represents a new therapeutic target. *PLoS One* **8**, e69354, doi:10.1371/journal.pone.0069354 (2013).
217 Takashima, M. *et al.* Overexpression of alpha enolase in hepatitis C virus-related hepatocellular carcinoma: association with tumor progression as determined by proteomic analysis. *Proteomics* **5**, 1686-1692, doi:10.1002/pmic.200401022 (2005).
218 Hamaguchi, T. *et al.* Glycolysis module activated by hypoxia-inducible factor 1α is related to the aggressive phenotype of hepatocellular carcinoma. *International Journal of Oncology* **33**, 725-731, doi:10.3892/ijo_00000058 (2008).
219 Capello, M., Ferri-Borgogno, S., Cappello, P. & Novelli, F. alpha-Enolase: a promising therapeutic and diagnostic tumor target. *FEBS J* **278**, 1064-1074, doi:10.1111/j.1742-4658.2011.08025.x (2011).
220 Gonzalez-Rodriguez, P. *et al.* SETD2 mutation in renal clear cell carcinoma suppress autophagy via regulation of ATG12. *Cell Death Dis* **11**, 69, doi:10.1038/s41419-020-2266-x (2020).
221 Mar, B. G. *et al.* Mutations in epigenetic regulators including SETD2 are gained during relapse in paediatric acute lymphoblastic leukaemia. *Nat Commun* **5**, 3469, doi:10.1038/ncomms4469 (2014).
222 Viaene, A. N. *et al.* SETD2 mutations in primary central nervous system tumors. *Acta Neuropathol Commun* **6**, 123, doi:10.1186/s40478-018-0623-0 (2018).
223 Zheng, X. *et al.* SETD2 variation correlates with tumor mutational burden and MSI along with improved response to immunotherapy. *BMC Cancer* **23**, 686, doi:10.1186/s12885-023-10920-4 (2023).
224 Rabet, M. M. *et al.* Nectin-4: a new prognostic biomarker for efficient therapeutic targeting of primary and metastatic triple-negative breast cancer. *Ann Oncol* **28**, 769-776, doi:10.1093/annonc/mdw678 (2017).

225 Rogmans, C. *et al.* Nectin-4 as Blood-Based Biomarker Enables Detection of Early Ovarian Cancer Stages. *Cancers (Basel)* **14**, doi:10.3390/cancers14235867 (2022).
226 Chang, H. K. *et al.* Nectin-4 as a Predictive Marker for Poor Prognosis of Endometrial Cancer with Mismatch Repair Impairment. *Cancers (Basel)* **15**, doi:10.3390/cancers15102865 (2023).
227 Lartigue, J. d. *Nectin-4 Emerges as a Therapeutic Target in Urothelial Carcinoma and Beyond*, <https://www.onclive.com/view/nectin-4-emerges-as-a-therapeutic-target-in-urothelial-carcinoma-and-beyond> (
228 Rodler, S. *et al.* Expression of Nectin-4 in Variant Histologies of Bladder Cancer and Its Prognostic Value-Need for Biomarker Testing in High-Risk Patients? *Cancers (Basel)* **14**, doi:10.3390/cancers14184411 (2022).
229 Liu, Y. *et al.* Role of Nectin-4 protein in cancer (Review). *Int J Oncol* **59**, doi:10.3892/ijo.2021.5273 (2021).
230 Chatterjee, S., Sinha, S. & Kundu, C. N. Nectin cell adhesion molecule-4 (NECTIN-4): A potential target for cancer therapy. *Eur J Pharmacol* **911**, 174516, doi:10.1016/j.ejphar.2021.174516 (2021).
231 Zhang, Z. *et al.* Prognostic and Immunological Role of Gasdermin E in Pan-Cancer Analysis. *Front Oncol* **11**, 706266, doi:10.3389/fonc.2021.706266 (2021).
232 Kim, M. S. *et al.* Methylation of the DFNA5 increases risk of lymph node metastasis in human breast cancer. *Biochem Biophys Res Commun* **370**, 38-43, doi:10.1016/j.bbrc.2008.03.026 (2008).
233 Ibrahim, J., Op de Beeck, K., Fransen, E., Peeters, M. & Van Camp, G. The Gasdermin E Gene Has Potential as a Pan-Cancer Biomarker, While Discriminating between Different Tumor Types. *Cancers (Basel)* **11**, doi:10.3390/cancers11111810 (2019).
234 Cao, J., Yan, W., Ma, X., Huang, H. & Yan, H. Insulin-like Growth Factor 2 mRNA-Binding Protein 2-a Potential Link Between Type 2 Diabetes Mellitus and Cancer. *J Clin Endocrinol Metab* **106**, 2807-2818, doi:10.1210/clinem/dgab391 (2021).
235 Cao, J., Mu, Q. & Huang, H. The Roles of Insulin-Like Growth Factor 2 mRNA-Binding Protein 2 in Cancer and Cancer Stem Cells. *Stem Cells Int* **2018**, 4217259, doi:10.1155/2018/4217259 (2018).
236 Zhu, T. Y., Hong, L. L. & Ling, Z. Q. Oncofetal protein IGF2BPs in human cancer: functions, mechanisms and therapeutic potential. *Biomark Res* **11**, 62, doi:10.1186/s40364-023-00499-0 (2023).
237 Lawlor, R. T. *et al.* Tumor Mutational Burden as a Potential Biomarker for Immunotherapy in Pancreatic Cancer: Systematic Review and Still-Open Questions. *Cancers (Basel)* **13**, doi:10.3390/cancers13133119 (2021).
238 Jardim, D. L., Goodman, A., de Melo Gagliato, D. & Kurzrock, R. The Challenges of Tumor Mutational Burden as an Immunotherapy Biomarker. *Cancer Cell* **39**, 154-173, doi:10.1016/j.ccell.2020.10.001 (2021).
239 He, Y. *et al.* The prognostic value of autophagy-related markers beclin-1 and microtubule-associated protein light chain 3B in cancers: a systematic review and meta-analysis. *Tumour Biol* **35**, 7317-7326, doi:10.1007/s13277-014-2060-4 (2014).

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Author contributions

J.M.I. performed NLP-based data analysis, K.A.I. extracted insights from NLP-data and generated the Trend Landscape Map, K.A.I. and R.T. prepared figures, K.A.I., J.M.I., R.T., K.R., Y.R., J.M.S., S.A.S., Q.A.Z. contributed to writing, reviewing, and editing of the manuscript.

Competing interests

The authors declare no competing interests.