BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 32(1), 13-24 (2024)

Current Development Status of Cytokines for Cancer Immunotherapy

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Abstract

Cytokines influence the overall cancer immune cycle by triggering tumor antigen expression, antigen presenting, immune cell priming and activation, effector immune cell recruitment and infiltration to cancer, and cancer killing in the tumor microenvironment (TME). Therefore, cytokines have been considered potential anti-cancer immunotherapy, and cytokine-based anti-cancer therapies continue to be an active area of research and development in the field of cancer immunotherapy, with ongoing clinical trials exploring new strategies to improve efficacy and safety. In this review, we examine past and present clinical developments for major anticancer cytokines, including interleukins (IL-2, IL-15, IL-12, IL-21), interferons, TGF-beta, and GM-CSF. We identify the current status and changes in the technology platform being applied to cytokine-based immune anti-cancer therapeutics. Through this, we discuss the opportunities and challenges of cytokine-based immune anti-cancer treatments in the current immunotherapy market and suggest development directions to enhance the clinical use of cytokines as immuno-anticancer drugs in the future.

Key Words: Cytokine, Cancer, Immunotherapy, Clinical trials

INTRODUCTION

Cytokines are small proteins, typically ranging from 5 to 25 kDa in size, primarily produced by immune cells in response to infection, inflammation, injury, or various stimuli (Saenz *et al*., 2008) They are also produced by a variety of other cells, including fibroblasts, epithelial cells, endothelial cells, and stromal cells (Goldstein and Laszlo, 1988; Dranoff, 2004). Cytokines mediate cell-cell communication and play a crucial role in promoting immunity, as well as in promoting or inhibiting cell differentiation and proliferation (Floros and Tarhini, 2015). They also have an important role within the tumor microenvironment (TME), where they coordinate immune and inflammatory responses. Due to their regulatory effects on the immune system and their impact on tumor progression in the TME, certain cytokines have been recognized as potential cancer immunotherapies. They achieve this by modulating the host immune response toward cancer cells and by directly exhibiting anti-cancer activities, such as anti-proliferation and induction of apoptosis. In fact, cytokines have a long history as anti-cancer drugs, dating back to the 1970s, with interferon (IFN)-alpha and interleukin (IL)-2 being the first cytokines used for cancer therapy (Fyfe *et al*., 1995; Isaacs and Lindenmann, 1988).

Since then, numerous preclinical experiments and studies have confirmed the anti-cancer activity of cytokines. Several cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-gamma (IFNγ), IL-7, IL-12, and IL-21, are undergoing clinical trials (Sim and Radvanyi, 2014; Floros and Tarhini, 2015; Waldmann, 2018). However, despite receiving FDA approval as a cancer immunotherapy and subsequent research findings, cytokine-based immunotherapy is not as widely utilized in clinical settings as immune checkpoint inhibitors, which have been extensively researched and developed in the meantime. Many hurdles for the clinical use of anti-cancer cytokine therapy still need to be overcome in terms of side effects versus effectiveness. Despite these challenges, research on many immune anti-cancer cytokines continues, and development is in progress. The purpose of this article is to review current development trends in cytokines for anticancer immunotherapy by examining clinical trials of anti-cancer cytokines registered on the ClinicalTrials.gov website. Through this analysis, we aim to evaluate the opportunities and challenges in the cytokine-based anticancer immunotherapy market for practical clinical applications. Additionally, we discuss the direction for the development of cytokines for

Open Access **https://doi.org/10.4062/biomolther.2023.196**

Received Nov 6, 2023 **Revised** Dec 6, 2023 **Accepted** Dec 6, 2023
Published Online Jan 1, 2024

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anticancer immunotherapy.

THE CURRENT DEVELOPMENT TRENDS OF CYTOKINES FOR ANTI-CANCER IMMUNOTHERAPY

We have analyzed the current clinical trial status of 10 cytokine therapies, including ILs (IL-2, IL-15, IL-12, IL-21), IFNs (alpha, beta, gamma, lambda), TGF-beta, and GM-CSF, by examining the ongoing clinical trials of each cytokine registered on the ClinicalTrials.gov website as of June 08, 2023. The extracted cytokines are categorized as either cancer-related or non-cancer-related based on the clinical trial indications (Fig. 1A). The most active clinical trials have been conducted on interferon, followed by IL-2, GM-CSF, TGF-beta, IL-12, and IL-15. Among these, clinical trials targeting cancer appeared in the following order: IL-2, GM-CSF, IFNs, IL-12, TGF-beta, and IL-15. Except for IL-21, clinical trials for each cytokine mainly focused on the development of anticancer drugs, accounting for more than 60% of indications. IL-21 is being developed as cancer therapies in clinical trials at rates of 45%. The most active development among anti-cancer cytokines is being carried out for IL-2, GM-CSF, and IFNs in that order, with 568, 546, and 392 clinical trials of anti-cancer cytokines conducted, respectively. Even though the first anti-cancer cytokine was developed up to the 1970s, the substantial development of anti-cancer cytokines was focused on cytokines such as IL-2, GM-CSF, and IFNs until before the year 2000, in conjunction with the interest in cancer immunotherapy. With the increasing interest in immunotherapies for cancer, it can be observed that active research on cytokines like IL-12 and IL-15 also began after 2015 (Supplementary Fig. 1). The development of interferon as an anticancer cytokine appears to have gradually decreased since the period 2000–2004, and similarly, the development of GM-CSF has also tended to decrease since 2015–2019. Although the absolute number of clinical trials is still small, the development of IL-2, IL-15, and TGF-beta shows a continuous increasing trend during the period 2010–2014.

Anticancer cytokines were primarily developed for indications such as hematological cancer, pan-oncology, melanoma, renal cell carcinoma, neuroblastoma/glioblastoma, and breast cancer (Fig. 1B). While certain cytokines, like interferons, exhibit direct anticancer effects through anti-proliferative actions, the majority of anticancer cytokines do not specifically target cancer cells. Instead, they act on the broader tumor microenvironment and are consequently developed for pan-tumor indications. Due to their low direct cytotoxicity against cancer cells, most clinical trials actively use cytokines in combination with other treatments rather than alone (Fig. 1C). It was confirmed that the goal of these clinical trials is to maximize the treatment effect by combining cytokines with existing treatments rather than using them as a single agent. Additionally, cytokines are primarily being developed as therapeutic agents that provide anticancer effects through agonists other than TGF-beta in the tumor microenvironment (Fig. 1D).

INTERLEUKIN-2 (IL-2)

IL-2 is a currently leading cytokine for development of anticancer immunotherapy. IL-2 is a 15.5 kDa small glycosylated protein with four bundle α-helical structure, which is mainly produced by antigen-activated CD4 + and CD8+ T help cells, although, naïve T cells, NK cells and dendritic cells also can produce (Ruscetti, 1984). Secreted IL-2 binds to the allosteric receptor complex with the three distinct subunits, IL-2R α (CD25), IL-2R β (CD122), and common-γ chain (CD132) which mainly express on activated T-lymphocytes, regulatory T cells, mature DCs and B cell (Cheng *et al*., 2002; Wang *et al*., 2009; Skrombolas and Frelinger, 2014). The effect of IL-2 is dependent on IL-2 level in which low level IL2 primarily promote the differentiation of CD4+T cell into follicular helper or central memory T cells. Especially IL-2 plays a critical role in differentiation, expansion and activation of effector CD8+ T cell and NK cell in tumor microenvironment, resulting in anticancerous effect. IL-2 was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma and after that for metastatic melanoma in 1998. Since then, IL-2 has been continuously developed as an immune-anticancer cytokine for various cancer types (Fig. 2A, 2B).

Until 2000, more than 90% were developed in the form of natural IL-2, but since 2000s, development in the form of fusion protein or immunocytokine has been steadily progressing (Fig. 2C, 2D). In this review, the immunocytokine, a fusion protein combining a cancer-targeting antibody or fragment antibody with a cytokine, was classified separately from other fusion proteins due to the identification of various types of immunocytokines. Fusion protein or Immunocytokine platforms provide a good strategy for elongating half-life and minimizing toxicity through targeted approaches against cancer. Overall, since the 2020s, the development of natural or mutein forms of IL-2 has tended to noticeably decrease, while the application of various technologies is gradually increasing in IL-2. The development of mutein forms with altered IL-2 sequences has been actively progressing before 2020. To maximize the activity of IL-2, IL-2 mutants primarily modulate affinity with the IL-2R β and γ receptors higher, while showing lower affinity with IL-2Rα. It appears that technology is being developed to continuously improve drug efficacy by combining IL-2 muteins with fusion proteins or immunocytokine forms. Additionally, the development of drugs in the form of pegylation, the advancement of prodrug technology through this pegylation, and the integration of technologies with cell and gene treatments, representing cutting-edge biopharmaceuticals, indicate a trend toward a significant increase in the proportion of overall IL-2 clinical trials after 2020.

INTERLEUKIN-12 (IL-12)

IL-12 is a 75 kDa cytokine consisting of two subunits, p40 and p35 (Kobayashi *et al*., 1989). It is thought to exhibit anticancer activity mainly by inducing the proliferation of NK cells and cytotoxic CD8+ T cells. However, IL-12 has limitations in clinical use because existing research results show a systemic inflammatory response and sometimes severe myelotoxicity and hepatotoxicity (Jenks, 1996). Among anti-cancer cytokines, IL-12 was not actively developed until 2010, but its development as an anticancer cytokine rapidly increased since then (Fig. 3A). In particular, it is noteworthy that more than half of the drugs are being developed mainly in the form of gene therapy since 2010 (Fig. 3B, 3C). Although IL-2 has experimentally demonstrated anti-cancer effects, its systemic administration through a recombinant protein in clinical trials

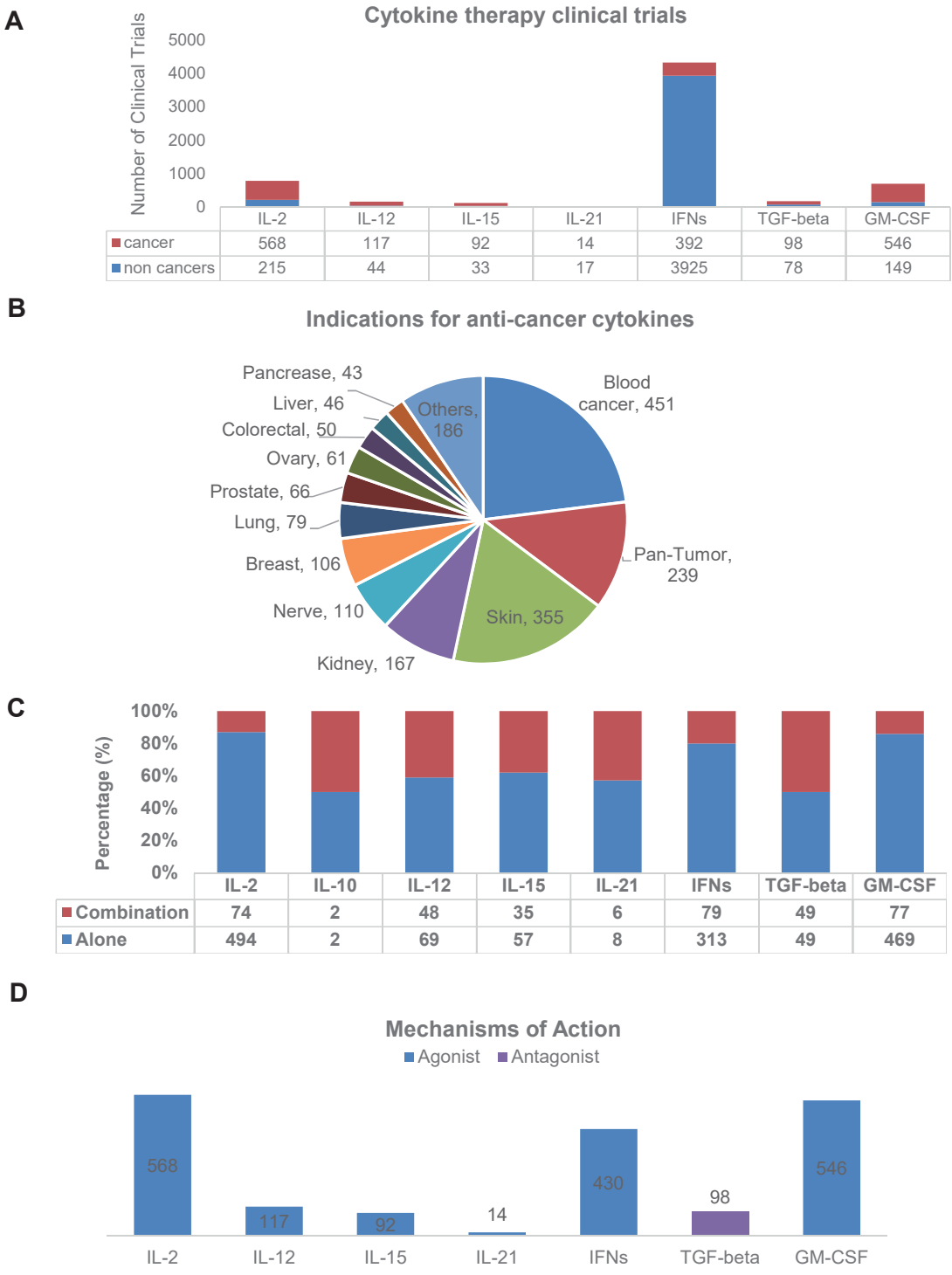
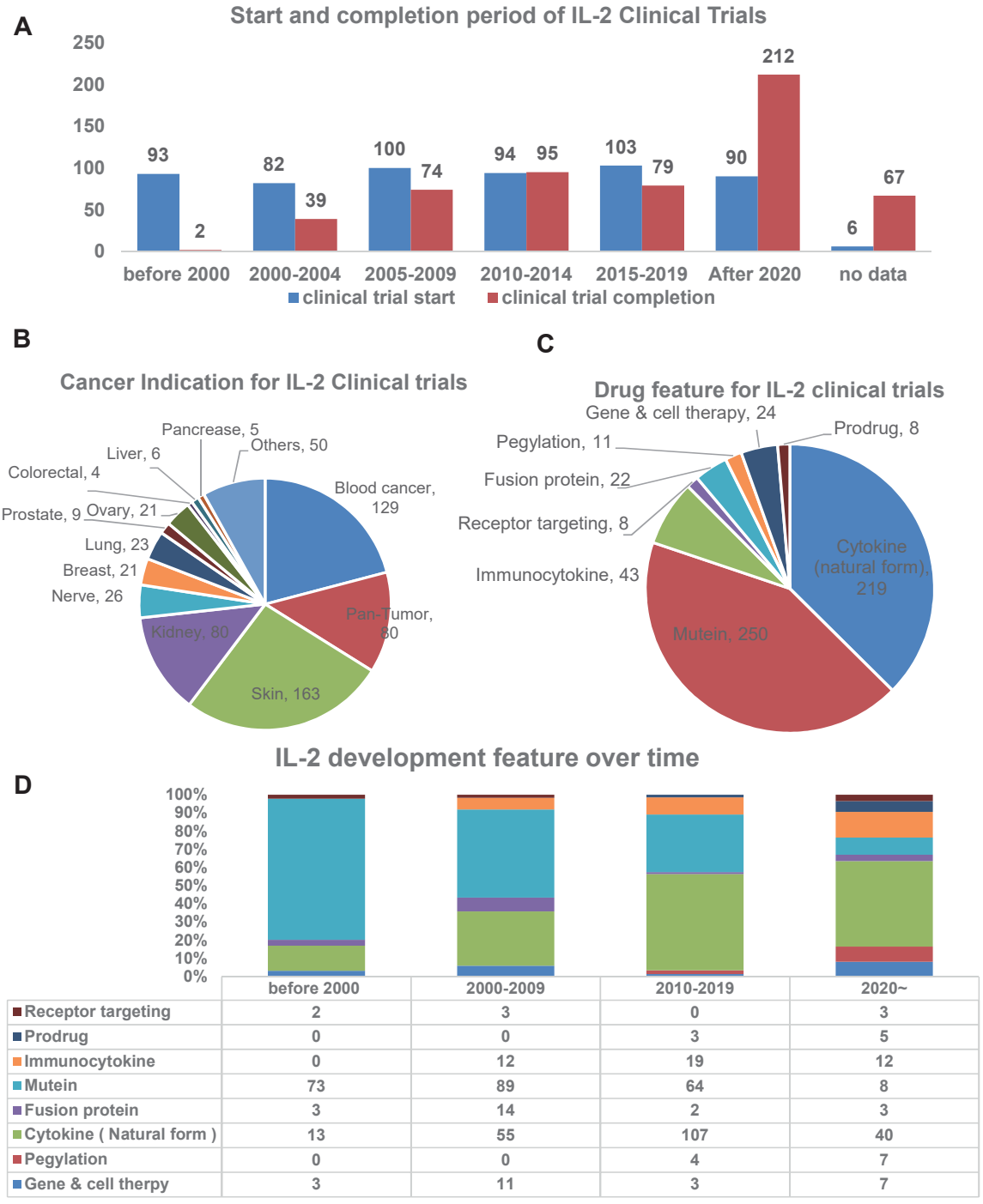


Fig. 1. Trends in Clinical Trials for Cytokines. (A) Number of clinical trials on major cytokines conducted or in progress. (B) Indications for anti-cancer cytokines. (C) Therapeutic strategy: combination or alone. (D) Mechanisms of action: agonist or antagonist.

yielded minimal efficacy at acceptable doses, accompanied by relatively high toxicity. Consequently, to address this issue, there is a belief that active efforts are underway to develop drug forms through gene therapy, aiming to deliver IL-12 localized to the tumor microenvironment to minimize systemic exposure. The introduction of these new technologies has led to a steady increase in the number of IL-12s entering clinical trials since 2005. With the localized delivery technology targeted at the tumor microenvironment, IL-12 seems to be developed with a greater emphasis on solid cancers rather than blood



	before 2000	2000-2009	2010-2019	2020~
Receptor targeting	2	3	0	3
Prodrug	0	0	3	5
Immunocytokine	0	12	19	12
Mutein	73	89	64	8
Fusion protein	3	14	2	3
Cytokine (Natural form)	13	55	107	40
Pegylation	0	0	4	7
Gene & cell therpy	3	11	3	7

Fig. 2. IL-2 Clinical Trials Development Trends. (A) Start and completion period of IL-2 clinical trials. (B) Cancer indications for IL-2 clinical trials. (C) Drug features for IL-2 clinical trials. (D) IL-2 development platform technology over time.

cancers when compared to other cytokines (Fig. 3D).

INTERLEUKIN-15 (IL-15)

IL-15 is one of the most promising potent anticancer cytokines. IL-15 is a 14~15kDa cytokine that plays a critical role in both innate and adaptive immune response. It can be stimulate the activity of immune cells. Like IL-2, IL-15 has a four alpha helix and shared the IL-2 receptor subunites, IL-2R β (CD122), and common-γ chain (CD132) with IL-2 (Budagian *et al*., 2006). Thus, the function of IL-15 present quite similar with IL-2 on lymphocytes and NK cells. Moreover, IL-15 considered more potent than IL-2 because of no effect on regulator

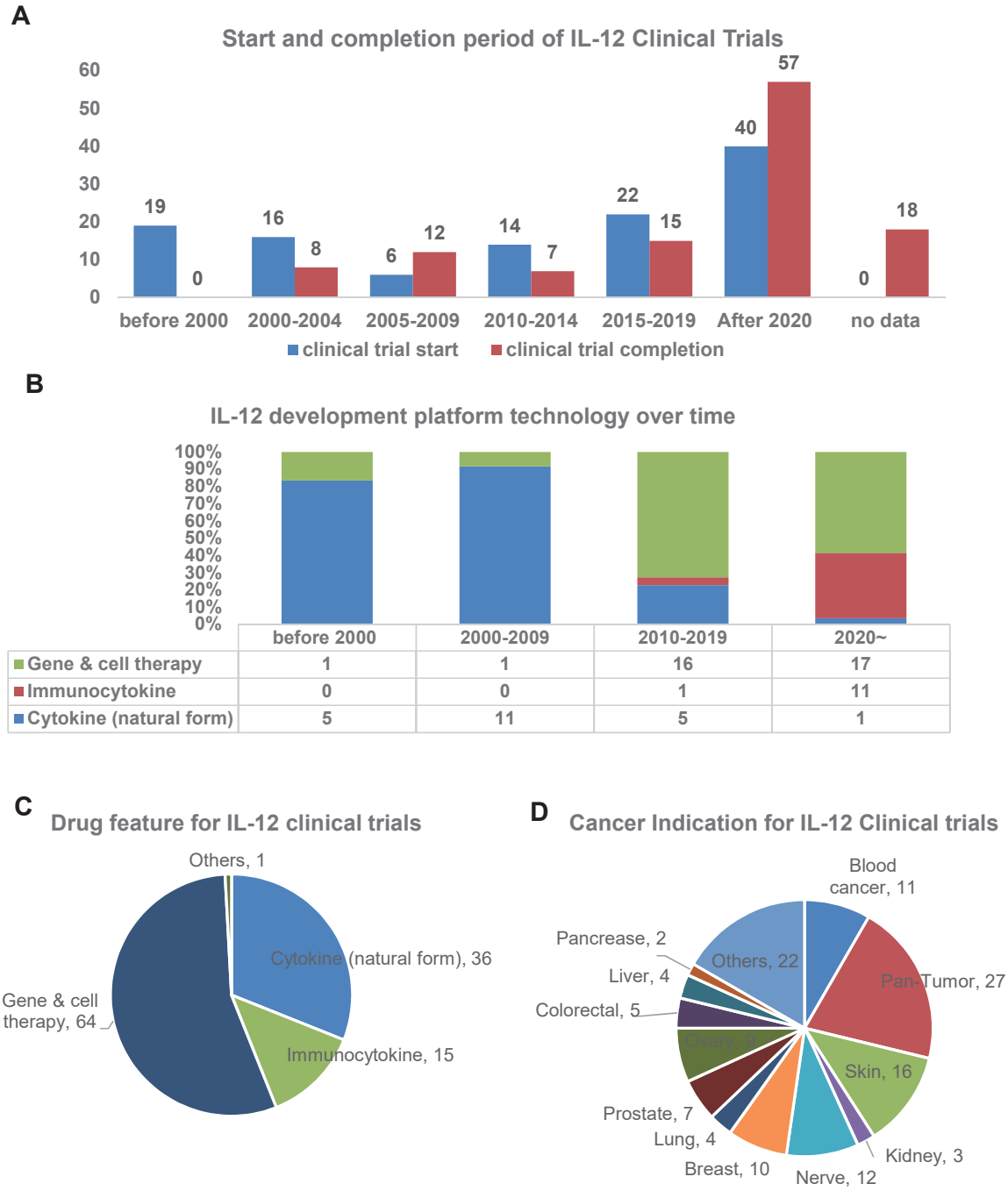


Fig. 3. IL-12 Clinical Trials Development Trends. (A) Start and completion period of IL-12 clinical trials. (B) Cancer indications for IL-12 clinical trials. (C) Drug features for IL-12 clinical trials. (D) IL-12 development platform technology over time.

T cell while IL-2 promotes the development and maintenance of CD25+ Foxp3 T regulatory cells (Waldmann, 2004). One of the key downstream targets of the JAK/STAT pathway activated by IL-15 is natural killer (NK) cells (Mishra *et al*., 2014). IL-15 can enhance the proliferation and cytotoxicity of NK cells by upregulating the expression of molecules such as perforin and granzyme B, which can induce apoptosis in cancer cells. IL-15 can also activate other immune cells such as cytotoxic CD8+ and memory T cells and dendritic cells, which can contribute to the anti-tumor response. Like IL-12, IL-15 has been actively developed since 2010 and is being applied to hematological cancers and various solid tumors (Fig. 4A, 4B). Various technology platforms have been employed for the development of the anti-cancer cytokine IL-15 since 2010, with a relative decrease in the development of natural IL-15. Specifically, the primary forms of development actively involve creating fusion proteins that combine IL-15 mutein and Fc, as well as gene cell therapy that induces the expression of IL-15

	before 2000	2000-2009	2010-2019	2020~
Antibody	0	2	0	0
Immunocytokine	0	0	0	4
Mutein	0	0	34	7
Fusion protein	0	0	36	9
Cytokine (Natural form)	0	1	13	2
Pegylation	0	0	1	2
Gene & cell therpy	0	0	5	17

Fig. 4. IL-15 Clinical Trials Development Trends. (A) Start and completion period of IL-15 clinical trials. (B) Cancer indications for IL-15 clinical trials. (C) Drug features for IL-15 clinical trials. (D) IL-15 development platform technology over time.

in CAR-NK cells (Fig. 4C, 4D).

INTERLEUKIN-21 (IL-21)

IL-21 is a cytokine which also share a common gamma receptor with IL-2 and IL-15 (Spolski and Leonard, 2008; Sondergaard and Skak, 2009). IL-21 promote B cell differentiation into plasma cells, regulates immunoglobulin production, controls the proliferation and/or effector function of both CD4+ and CD8+ T cells and limits the differentiation of Tregs (Jauch *et al*., 2011; Stolfi *et al*., 2011). It has gained considerable attention as a potential anti-cancer immunotherapy due to its ability to stimulate the immune system and enhance anti-tu-

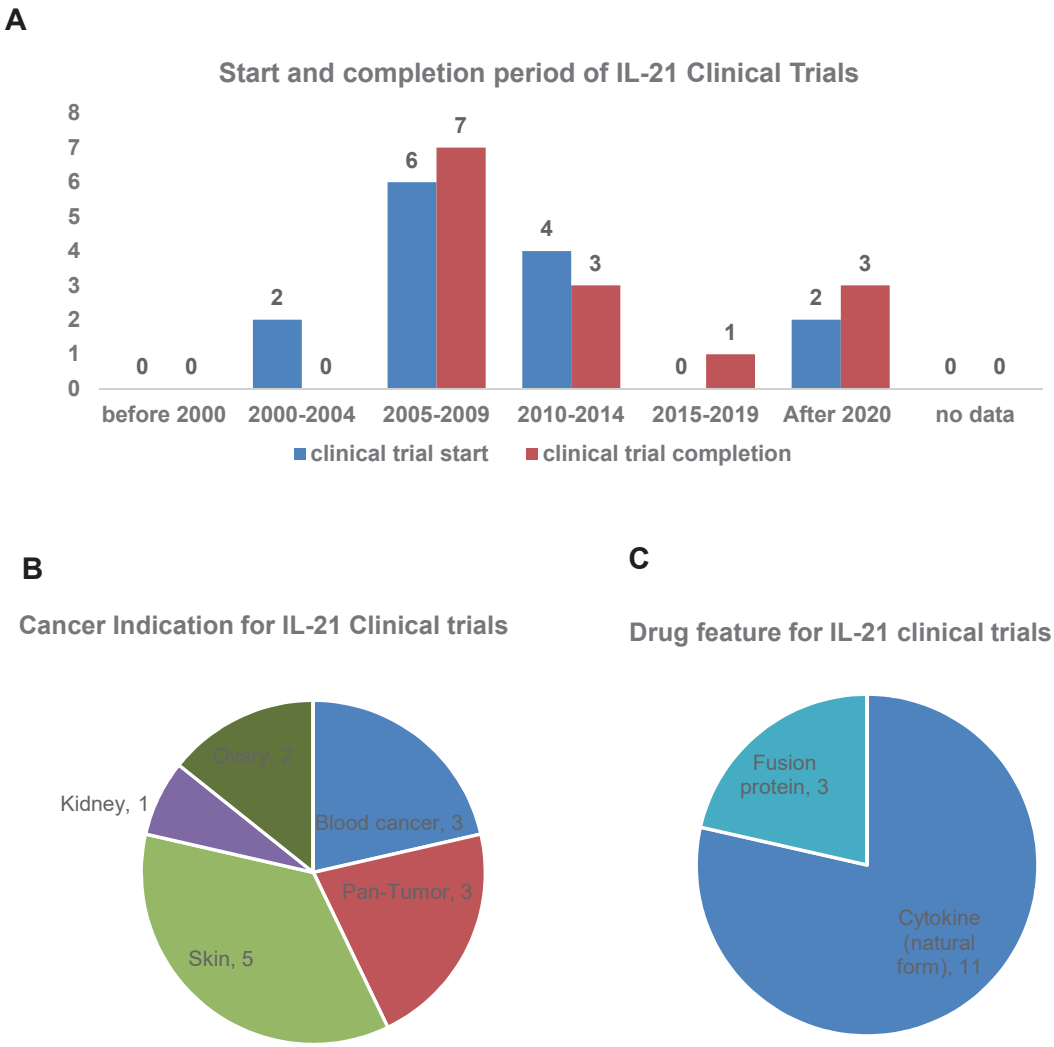
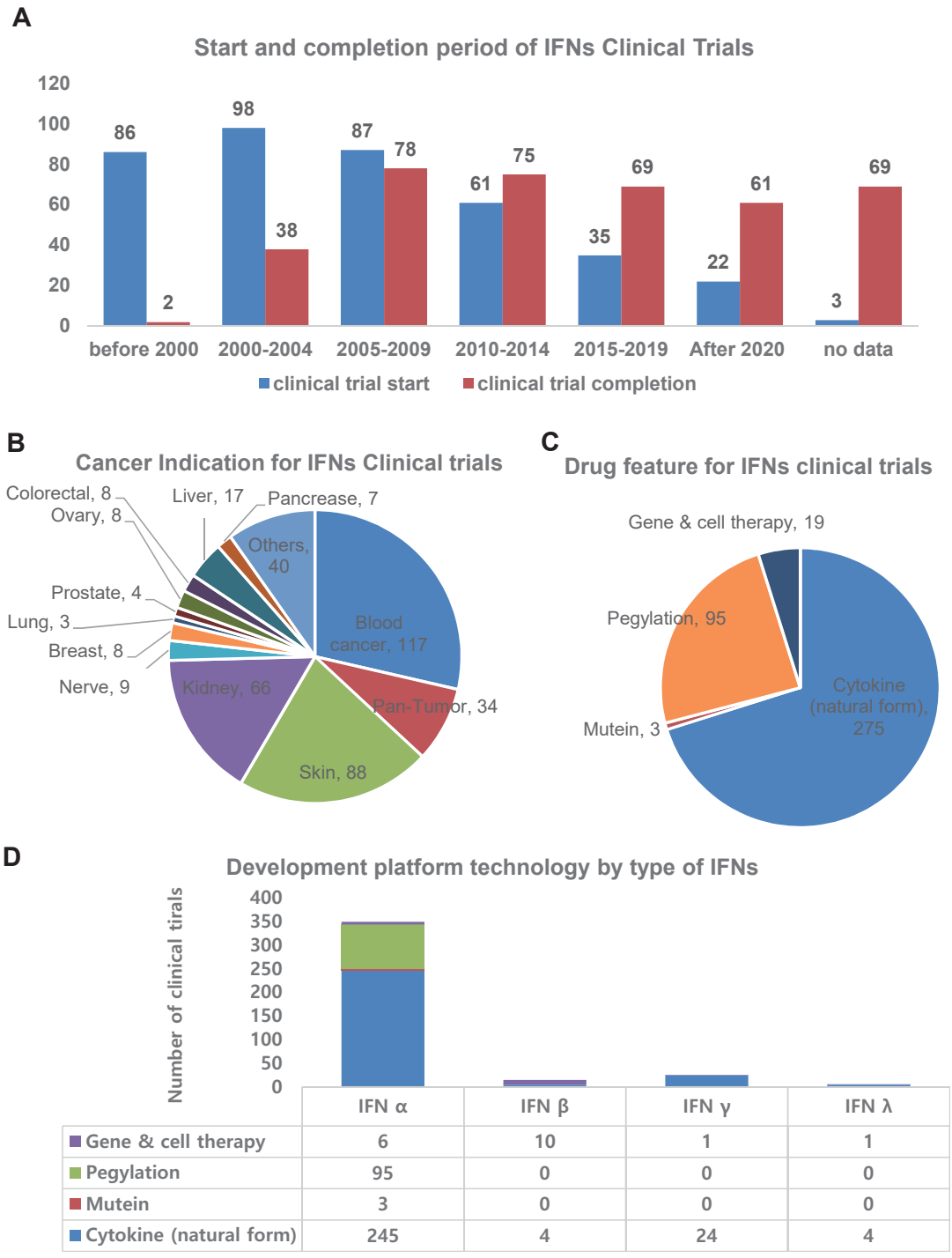


Fig. 5. IL-21 Clinical Trials Development Trends. (A) Start and completion period of IL-21 clinical trials. (B) Cancer indication for IL-21 clinical trials. (C) Drug feature for IL-21 clinical trials.

mor responses. The clinical development of IL-21 as an anti-tumor drug is not progressing as actively as compared to other cytokines. In the case of IL21, clinical development began in 2004, and as of July 2023, as with other anti-tumor cytokines, a total of 14 clinical trials were conducted with the main indications being hematological cancer, pan-tumor, melanoma, and renal cell carcinoma (Fig. 5A, 5B). Of these, 11 cases used the natural form of IL21, and in 3 cases, IL-21 in the form of a fusion protein with albumin is being developed (Fig. 5C).

INTERFERONS (IFNS)

IFNs are cytokines with a long history as an anticancer agent. They are largely divided into three types: Type I, which includes IFN-α, IFN-β, IFN-ω, and IFN-τ; Type II, which includes IFN-gamma; and the most recently recognized Type III, which includes IFN-λ (Katze *et al*., 2002). IFN-alpha was the first approved anticancer cytokine by the US Food and Drug Administration (FDA) in 1986 for the treatment of hairy cell leukemia. Since then, IFN-alpha has been applied in patients with chronic myeloid leukemia and several solid tumors, such as melanoma and renal cancer, as well as hairy cell leukemia. We found that IFN has been the third most actively clinically tested following IL-2 and GM-CSF (Fig. 1A). However, since the early 2000s, clinical trials for interferon for cancer indications have continued to decline significantly compared to other cytokines (Fig. 6A). Cancer indications did not show much difference from other cytokines, mainly involving hematological cancer, pan-oncology, melanoma, and renal cell carcinoma (Fig. 6B). Although the application of cell therapy or gene therapy technology was confirmed in about 19 clinical trial cases, almost all other clinical trials have been developed in the form of natural cytokines. Next to natural forms of interferon, pegylation on IFN was a platform technology mainly applied to increase the half-life of interferon and improve efficacy in clinical trials. Among the IFNs, IFN-alpha was mainly used in anticancer clinical trials (n=349), and natural interferon-gamma also was being developed as an anticancer cytokine (n=25) (Fig. 6C, 6D). Interferon-gamma belongs to Type II IFNs and



	IFN α	IFN β	IFN γ	IFN λ
Gene & cell therapy	6	10	1	1
Pegylation	95	0	0	0
Mutein	3	0	0	0
Cytokine (natural form)	245	4	24	4

Fig. 6. IFNs Clinical Trials Development Trends. (A) Start and completion period of IFNs clinical trials. (B) Cancer indications for IFNs clinical trials. (C) Drug features for IFNs clinical trials. (D) Development platform technology by type of IFNs.

activates the JAK/STAT signaling pathway in a manner similar to Type I interferons, inhibiting cell proliferation and inducing apoptosis (programmed cell death) and cell cycle arrest in cancer cells. IFN-beta is being developed as an anticancer cytokine (n=14), and the application of gene cell therapy technology (n=10) was relatively high in IFN-beta anticancer clinical trials. The remaining four cases of the IFN-beta anticancer clinical trials were developed as the natural form of IFN-beta.

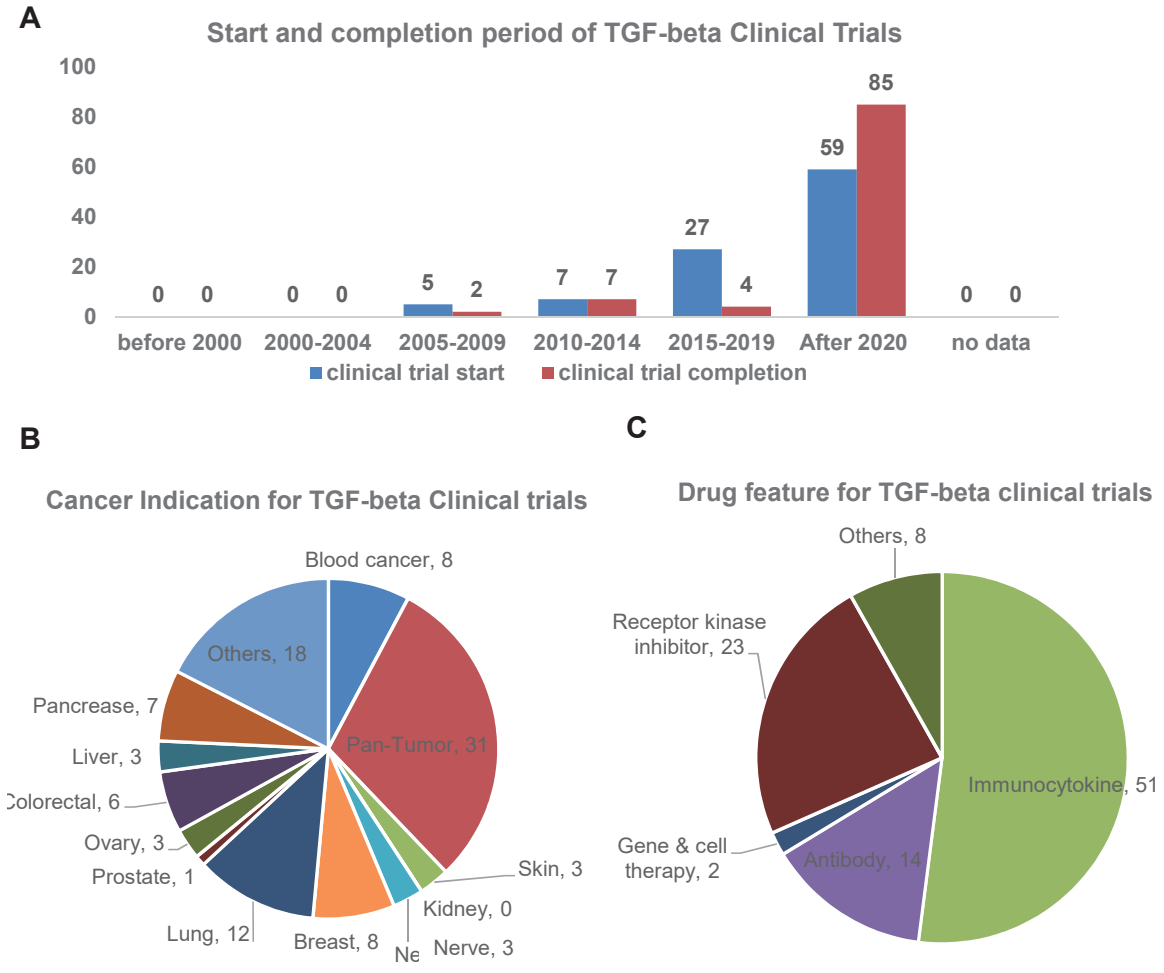


Fig. 7. TGF-beta Clinical Trials Development Trends. (A) Start and completion period of TGF-beta clinical trials. (B) Cancer indications for TGF-beta clinical trials. (C) Drug features for TGF-beta clinical trials.

TRANSFORMING GROWTH FACTOR-BETA (TGF-BETA)

TGF-beta is secreted by numerous cancer cells and plays a crucial role in cancer progression by participating in cancer proliferation and tumor microenvironment (TME) immunity (MaruYama *et al*., 2022). Consequently, TGFβ induces properties of cancer cell invasiveness, metastatic stem cells, and treatment resistance. Specifically, TGF-beta contributes to the generation of regulatory T cells in the TME, which promote anti-tumor immunosuppression. Therefore, inhibiting TGFβ signaling is considered essential and a key method to enhance the efficacy of current and future immunotherapies. Consequently, for its anticancer efficacy, TGF-beta stands out as the only anticancer cytokine being developed as an antagonist among the cytokines covered in this review (Fig. 1D). TGF-beta has been actively undergoing clinical trials since 2015, primarily for pan-tumor indications (Fig. 7A, 7B). Over 66% of these trials focus on the development of anti-TGF-beta antibodies and immunocytokines (Fig. 7C). Notably, clinical trials utilizing chemical agents to inhibit the activity of TGF-beta receptor kinase account for 23% of TGF-beta-related cancer tumor cytokine trials.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM- CSF)

GM-CSF is a cytokine that drives the generation of myeloid cell subsets including neutrophil, monocyte, macrophage, and dendritic cells in tumor microenvironments. Clinical trials for GM-CSF tended to increase steadily until 2010 but have decreased noticeably since then (Fig. 8A). The anti-tumor indications did not differ significantly from other cytokine clinical trials (Fig. 8B). As an anti-tumor cytokine, approximately 80% of clinical trials related to GM-CSF have been developed using natural cytokines, while the remaining 20% have been formulated as cell gene therapeutics (Fig. 8C). In particular, 222 out of the 546 GM-CSF clinical trials have used GM-CSF to enhance cancer immunity or activate vaccination.

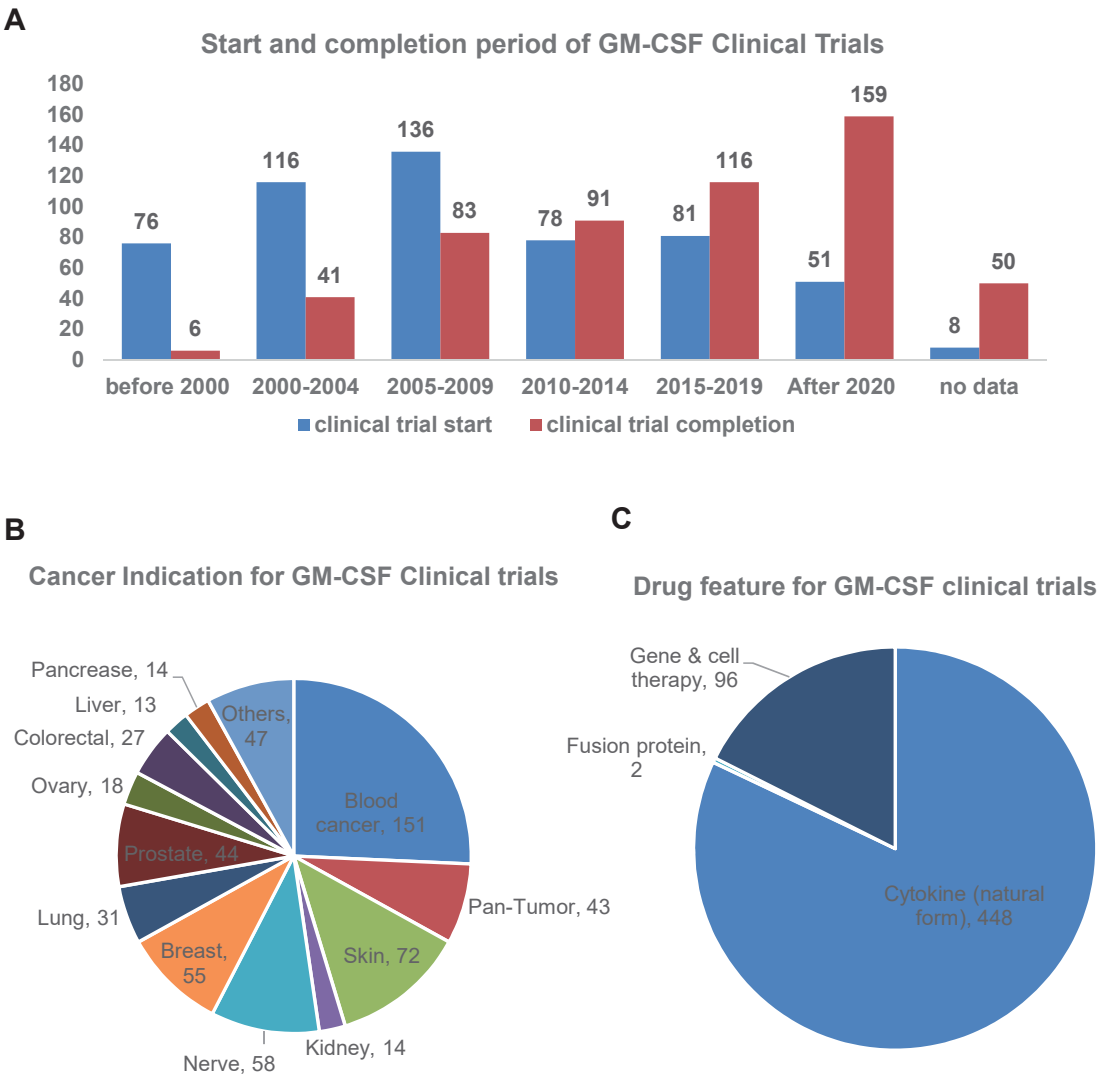


Fig. 8. GM-CSF Clinical Trials Development Trends. (A) Start and completion period of GM-CSF clinical trials. (B) Cancer indications for GM-CSF clinical trials. (C) Drug features for GM-CSF clinical trials.

CHALLENGES AND OPPORTUNITIES OF CYTOKINE AS ANTICANCER THERAPY

Cancer immunotherapy, centered on immune check point inhibitors (ICI), is a significant achievement in the field of cancer treatment because it can achieve successful effects by targeting the tumor microenvironment beyond drug therapy that directly targets cancer (Bernard-Tessier *et al*., 2018; Antonia *et al*., 2019; Fradet *et al*., 2019; Saka *et al*., 2021). However, contrary to expectations, it is not showing a wide range of general-purpose anticancer effects. Even in advanced carcinoma, the ICI response rate of antitumor response is as low as 20-30% of treated patients (Armand *et al*., 2018). Currently, the development of cancer immunotherapeutics that are applicable to more patients and various types is becoming an important topic in the cancer treatment market. In that respect, it is thought that cytokine- anti-cancer therapy, which can exhibit various effects on TME, can be a solution.

However, cytokine anti-cancer therapy could encounter challenges in clinical application. One primary factor restricting the clinical use of cytokine therapy is the complexity of the immune response to cytokines. The mechanisms of action and interactions of cytokines are not fully understood. Cytokine networks can display high redundancy, wherein multiple cytokines often activate the same downstream pathways. Additionally, cytokines can exert pleiotropic effects, simultaneously regulating multiple cellular functions in the tumor microenvironment (TME), making their actions highly complex. Even the same cytokine can demonstrate proliferative or antiproliferative effects depending on its interactions within its surroundings. While this complexity enables fine-tuned control of immune responses, it can result in insufficient effects due to compensatory mechanisms within tumor microenvironments. The systemic toxicity, such as vascular leakage syndrome, central nervous system toxicity, and cardiotoxicity, also poses problems and limits the use of adequate doses in clinical applications. Furthermore, the short half-life in the body not only

diminishes drug efficacy but also reduces patient compliance with frequent dosing.

Despite these limitations, anticancer cytokine treatments are emerging as a new frontier in anticancer immunotherapy. Various technology platforms are being employed to address issues associated with anti-cancer cytokines treatments. Going beyond genetic recombination technology such as immune-cytokine and fusion protein, the incorporation of cell gene therapy technology, classified as an advanced biopharmaceutical, is anticipated to play a crucial role in minimizing the side effects of anticancer cytokines and enhancing their activity. Specifically, the treatment's effectiveness is maximized when combined with existing therapies. Cytokine-based therapies have been combined with other treatments such as chemo-therapy, radiation therapy, targeted therapies and recently immune checkpoint inhibitors to improve their efficacy.

CONCLUSION

Cytokine-based immuno-anticancer therapy has been recognized as a promising approach for anti-cancer treatment. It targets the tumor microenvironment through various means, including the regulation of the host immune response and activation of the immune system. Sometimes, it can directly target the cancers (Larkin *et al*., 2019). However, several limitations persist in terms of drug efficacy and toxicity during clinical use. To address these challenges, clinical trials for anti-cancer cytokines have explored combination treatment strategies with various approaches. Additionally, through the integration of diverse technologies, such as the development of immunocytokines or fusion proteins, pegylation, prodrug design, and cell gene therapy technology, the anticancer efficacy of cytokines is increased, and side effects are minimized. These innovative approaches in cytokine anti-cancer immunotherapy hold the potential to successfully treat various blood cancers and solid tumors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This research was supported by Duksung Women`s University Research Grants 2021 (3000005804).

REFERENCES

Antonia, S. J., Borghaei, H., Ramalingam, S. S., Horn, L., De Castro Carpeno, J., Pluzanski, A., Burgio, M. A., Garassino, M., Chow, L. Q. M., Gettinger, S., Crinò, L., Planchard, D., Butts, C., Drilon, A., Wojcik-Tomaszewska, J., Otterson, G. A., Agrawal, S., Li, A., Penrod, J. R. and Brahmer, J. (2019) Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. *Lancet Oncol.* **20**, 1395-1408.

Armand, P., Engert, A., Younes, A., Fanale, M., Santoro, A., Zinzani, P. L., Timmerman, J. M., Collins, G. P., Ramchandren, R., Cohen, J. B., De Boer, J. P., Kuruvilla, J., Savage, K. J., Trneny, M., Shipp, M. A., Kato, K., Sumbul, A., Farsaci, B. and Ansell, S. M. (2018) Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J. Clin. Oncol.* **36**, 1428-1439.

Bernard-Tessier, A., Baldini, C., Martin, P., Champiat, S., Hollebecque, A., Postel-Vinay, S., Varga, A., Bahleda, R., Gazzah, A., Michot, J. M., Ribrag, V., Armand, J. P., Marabelle, A., Soria, J. C. and Massard, C. (2018) Outcomes of long-term responders to anti-programmed death 1 and anti-programmed death ligand 1 when being rechallenged with the same anti-programmed death 1 and anti-programmed death ligand 1 at progression. *Eur. J. Cancer* **101**, 160-164.

Budagian, V., Bulanova, E., Paus, R. and Bulfone-Paus, S. (2006) IL-15/IL-15 receptor biology: a guided tour through an expanding universe. *Cytokine Growth Factor Rev.* **17**, 259-280.

Cheng, L. E., Ohlen, C., Nelson, B. H. and Greenberg, P. D. (2002) Enhanced signaling through the IL-2 receptor in CD8+ T cells regulated by antigen recognition results in preferential proliferation and expansion of responding CD8+ T cells rather than promotion of cell death. *Proc. Natl. Acad. Sci. U. S. A.* **99**, 3001-3006.

Dranoff, G. (2004) Cytokines in cancer pathogenesis and cancer therapy. *Nat. Rev. Cancer* **4**, 11-22.

Floros, T. and Tarhini, A. A. (2015) Anticancer cytokines: biology and clinical effects of interferon-alpha2, interleukin (IL)-2, IL-15, IL-21, and IL-12. *Semin. Oncol.* **42**, 539-548.

Fradet, Y., Bellmunt, J., Vaughn, D. J., Lee, J. L., Fong, L., Vogelzang, N. J., Climent, M. A., Petrylak, D. P., Choueiri, T. K., Necchi, A., Gerritsen, W., Gurney, H., Quinn, D. I., Culine, S., Sternberg, C. N., Nam, K., Frenkl, T. L., Perini, R. F., de Wit, R. and Bajorin, D. F. (2019) Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann. Oncol.* **30**, 970-976.

Fyfe, G., Fisher, R. I., Rosenberg, S. A., Sznol, M., Parkinson, D. R. and Louie, A. C. (1995) Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J. Clin. Oncol.* **13**, 688-696.

Goldstein, D. and Laszlo, J. (1988) The role of interferon in cancer therapy: a current perspective. *CA Cancer J. Clin.* **38**, 258-277.

Isaacs, A. and Lindenmann, J. (1988) Classics in oncology: virus interference: I. the interferon. *CA Cancer J. Clin.* **38**, 280-290.

Jauch, D., Martin, M., Schiechl, G., Kesselring, R., Schlitt, H. J., Geissler, E. K. and Fichtner-Feigl, S. (2011) Interleukin 21 controls tumour growth and tumour immunosurveillance in colitis-associated tumorigenesis in mice. *Gut* **60**, 1678-1686.

Jenks, S. (1996) After initial setback, IL-12 regaining popularity. *J. Natl. Cancer Inst.* **88**, 576-577.

Katze, M. G., He, Y. and Gale, M., Jr. (2002) Viruses and interferon: a fight for supremacy. *Nat. Rev. Immunol.* **2**, 675-687.

Kobayashi, M., Fitz, L., Ryan, M., Hewick, R. M., Clark, S. C., Chan, S., Loudon, R., Sherman, F., Perussia, B. and Trinchieri, G. (1989) Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. *J. Exp. Med.* **170**, 827-845.

Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Lao, C. D., Cowey, C. L., Schadendorf, D., Wagstaff, J., Dummer, R., Ferrucci, P. F., Smylie, M., Hogg, D., Hill, A., Márquez-Rodas, I., Haanen, J., Guidoboni, M., Maio, M., Schöffski, P., Carlino, M. S., Lebbé, C., McArthur, G., Ascierto, P. A., Daniels, G. A., Long, G. V., Bastholt, L., Rizzo, J. I., Balogh, A., Moshyk, A., Hodi, F. S. and Wolchok, J. D. (2019) Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N. Engl. J. Med.* **381**, 1535-1546.

MaruYama, T., Chen, W. and Shibata, H. (2022) TGF-beta and cancer immunotherapy. *Biol. Pharm. Bull.* **45**, 155-161.

Mishra, A., Sullivan, L. and Caligiuri, M. A. (2014) Molecular pathways: interleukin-15 signaling in health and in cancer. *Clin. Cancer Res.* **20**, 2044-2050.

Ruscetti, F. W. (1984) Biology of interleukin-2. *Surv. Immunol. Res.* **3**, 122-126.

Saenz, S. A., Taylor, B. C. and Artis, D. (2008) Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adap-

tive immune responses at mucosal sites. *Immunol. Rev.* **226**, 172-190.
Saka, H., Nishio, M., Hida, T., Nakagawa, K., Sakai, H., Nogami, N., Atagi, S., Takahashi, T., Horinouchi, H., Takenoyama, M., Katakami, N., Tanaka, H., Takeda, K., Satouchi, M., Isobe, H., Maemondo, M., Goto, K., Hirashima, T., Minato, K., Yada, N. and Tamura, T. (2021) Five-year follow-up results from phase II studies of nivolumab in Japanese patients with previously treated advanced non-small cell lung cancer: pooled analysis of the ONO-4538-05 and ONO-4538-06 studies. *Jpn. J. Clin. Oncol.* **51**, 106-113.
Sim, G. C. and Radvanyi, L. (2014) The IL-2 cytokine family in cancer immunotherapy. *Cytokine Growth Factor Rev.* **25**, 377-390.
Skrombolas, D. and Frelinger, J. G. (2014) Challenges and developing solutions for increasing the benefits of IL-2 treatment in tumor therapy. *Expert Rev. Clin. Immunol.* **10**, 207-217.
Sondergaard, H. and Skak, K. (2009) IL-21: roles in immunopathology and cancer therapy. *Tissue Antigens* **74**, 467-479.
Spolski, R. and Leonard, W. J. (2008) Interleukin-21: basic biology and implications for cancer and autoimmunity. *Annu. Rev. Immunol.* **26**, 57-79.
Stolfi, C., Rizzo, A., Franze, E., Rotondi, A., Fantini, M. C., Sarra, M., Caruso, R., Monteleone, I., Sileri, P., Franceschilli, L., Caprioli, F., Ferrero, S., MacDonald, T. T., Pallone, F. and Monteleone, G. (2011) Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. *J. Exp. Med.* **208**, 2279-2290.
Waldmann, T. A. (2004) Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases. *Arthritis Res. Ther.* **6**, 174-177.
Waldmann, T. A. (2018) Cytokines in cancer immunotherapy. *Cold Spring Harb. Perspect. Biol.* **10**, a028472.
Wang, X., Lupardus, P., Laporte, S. L. and Garcia, K. C. (2009) Structural biology of shared cytokine receptors. *Annu. Rev. Immunol.* **27**, 29-60.