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Immunological Agents for Cancer Therapies

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ABSTRACT
Compared with previous standards of care (including chemotherapy, radiotherapy, and surgery), cancer immunotherapy has brought significant improvements for patients in terms of survival and quality of life. Immunotherapy has now firmly established itself as a novel pillar of cancer care, from the metastatic stage to the adjuvant and neoadjuvant settings in numerous cancer types. In this review article, we highlight how the history of cancer immunotherapy paved the way for discoveries that are now part of the standard of care. We also highlight the current pitfalls and limitations of cancer checkpoint immunotherapy and how novel research in the fields of personalized cancer vaccines, autoimmunity, the microbiome, the tumour microenvironment, and metabolomics is aiming to solve those challenges.

Key Words : Immune checkpoint inhibitors, personalized cancer vaccines, immune-related adverse events, microbiome studies, metabolomics.

I. INTRODUCTION

The field of immuno-oncology has been transformational in the care of cancer patients. William B. Coley, now widely accepted as the father of immunotherapy, first attempted to harness the power of the immune system for treating cancer in the late 19th century. As an orthopedic surgeon who operated on patients with bone sarcomas, he noticed that some patients with significant postoperative wound infections—a common occurrence when aseptic technique had not yet been optimized—would undergo spontaneous regression of their unresected tumours. Beginning in 1891, Coley injected more than a thousand patients with mixtures of live and inactivated bacteria such as Streptococcus pyogenes and Serratia marcescens with the hope of inducing sepsis and strong immune and antitumour responses. His cocktail of bacteria became widely known as “Coley’s toxin” and represents the first documented active cancer immunotherapy intervention. Coley achieved durable complete remissions in several types of malignancies, including sarcoma, lymphoma, and testicular carcinoma. However, the lack of a known mechanism of action for Coley’s toxin and the risks of deliberately infecting cancer patients with pathogenic bacteria caused oncologists to adopt surgery and radiotherapy as alternative standard treatments early in the 20th century,It would take more than half a century before a better understanding of the key mediators of sepsis would shed some light on the mechanisms of action of Coley’s toxin. Those mediators constitute a cytokine family including interleukins, interferons, and chemokines. Once again, the race was on to apply those novel discoveries to cancer therapy. Physicians and researchers achieved modest success with this novel approach, occasionally inducing clinical remissions with high-dose interleukin 2 (il-2) in metastatic renal cell carcinoma and debatable responses with interferon in stages iii and iv melanoma. Those modest successes were often counterbalanced with significant adverse events. Although novel methods of delivery such as pegylation would abate some of the toxicities, the sporadic and unpredictable immune responses seen with those therapies meant that only a small, carefully selected subgroup of cancer patients would benefit. The next revolutionary wave in cancer immunotherapy came with the better understanding of the process of immune surveillance, by which innate immune cells eliminate cancer cells. The recent discovery of T cell immune checkpoints, such as ctla-4 and PD-1, propelled the field of immuno-oncology into its current era and saw the awarding of the 2018 Nobel prize in Physiology or Medicine to Drs.Allison and

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Honjo. Those hardwired signals have the crucial task of maintaining a fine balance between immune surveillance against foreign pathogens or abnormal cells and autoimmunity. Blocking those T cell surface receptors results in enhanced autoimmunity that induces an immune response against tumours, but can also increase the chance of autoimmune reactions. In this review article, we highlight the current standards of care in cancer immunotherapy, with a strong focus on immune checkpoint inhibitors (icis), their limitations and pitfalls, and promising novel approaches[1,2,3].

Cancer-immunity cycle

In 2013, Chen and Mellman (2013) used the concept of "the Cancer-Immunity Cycle," which dissects the anticancer immune response process similar to the way the body mounts response toward any foreign antigens .The cycle starts with cross-presentation of cancer-associated antigens from cancer cells to the major histocompatibility complex (MHC) molecules on the antigen presenting cells (APCs). Cancer antigens encompass cancer neoantigens from genomic alterations (mutations, translocations, readthrough and frame shifts), cancer associated proteins normally expressed at immune privileged sites, viral proteins and others (Step 1). APCs, upon capturing of cancer antigens, migrate to secondary lymphoid organs (Step 2). Tese APCs prime and activate naïve T cells via MHC-antigen-T cell receptor (TCR) interaction, along with a hierarchy of costimulatory signals, such as the CD28/B7-1/2-mediated signaling (Step 3). Activated immune cells then enter the circulation system (step 4), infltrate into the tumor microenvironment (Step 5), recognize tumor cells through the interaction of the TCR and its cognate antigen presented on MHC of tumor cells (Step 6) and kill their target cancer cells (Step 7). After killing the targeted cancer cells, release of more tumor antigens further fuels the anti-cancer immunity cycle[4].

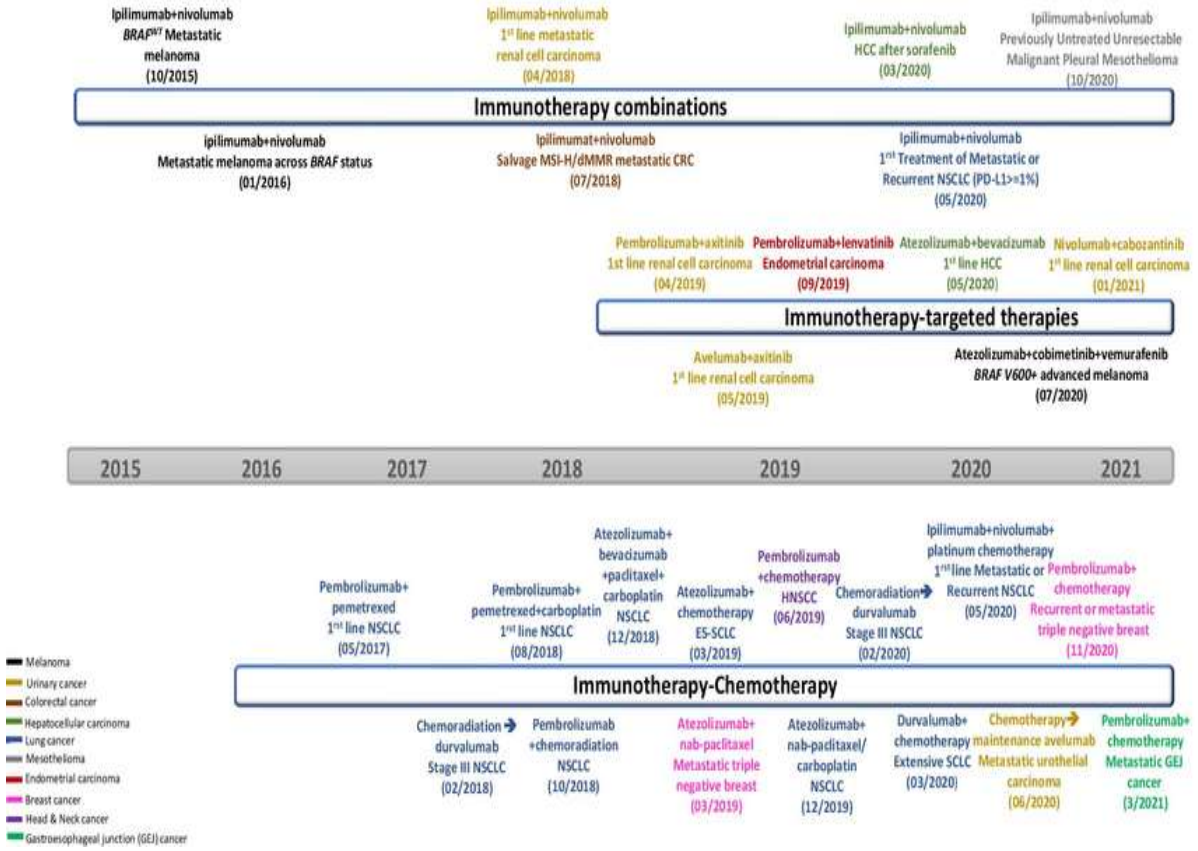

Fig .1 Timeline of the FDA approvals ofcombination therapy

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Fig. 2 The cancer-immunity cycle, resistant mechanisms and potential solutions

Resistant mechanisms along the cancer-immunity cycle

Cancer cells have been found to have intrinsic mechanisms bypassing every possible step along the cancerimmunity cycle to evade anti-cancer immunity .At the initiation of the anti-cancer immune response, some cancers with low tumor mutation burden or low immune cell infltration (such as in prostate cancer) may not elicit sufcient immune responses. Loss of MHC expression, loss or mutation of β2-microglobulin and mutations within the TCR binding domain of MHC have all been associated with escape from anti-cancer immunity. CTLA4 is the frst target of ICBs approved by the FDA .In addition to CTLA4, several other negative regulators such as T-cell immunoglobulin, mucin domaiprotein (TIM-3), lymphocyte-activation gene 3 (LAG-3), T-cell immunoreceptor tyrosine-based inhibition motif domain (TIGIT) and V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA), have been identifed and are currently being tested in clinical trials to determine their potential as targets for cancer immunotherapy. Other than negative regulators, suboptimal co-stimulation molecule expression, inefcient cytokine production and heightened infltration of immunosuppressive immune cells have all been found to contribute to weakened anti-cancer immunity. After immune cell priming and activation, any defects afecting immune cell trafcking, migration and infltration into the tumor microenvironment can invalidate anti-cancer immunity. Vascular endothelial growth factor (VEGF) plays important roles in angiogenesis as well as multiple facets of anti-cancer immunity. It decreases trafcking and

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extravasation of cytotoxic T cells, promotes infltration of Treg cells into the tumor bed and enhances the expression of PD-1 and other inhibitory checkpoints involved in CD8+T cell exhaustion. In mouse models, VEGF also impedes the commitment and progression of lymphoid progenitors to the T-cell lineage. Cytokines within the TME not only afect immune cell migration and recruitment to the tumor site, but also modulate immune cell activities. Some cytokines, such as Chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10 and CXCL11, elicit chemotactic function and attract cytotoxic T cells while other cytokines, as seen with CCL5, CCL17, CCL22 and CXCL8, attract myeloidderived suppressor cells (MDSCs) and Treg cells contributing to the immunosuppressive TME. In addition to cytokines, transforming growth factor beta (TGF-β) is a multipotent growth factor that afects cell growth and diferentiation, apoptosis and immunosuppression. It is present in high concentrations in the TME because of production by cancer, stromal and immune cells. In general, it inhibits anti-cancer immunity through inhibiting the function of efector immune cells and promoting suppressive cells . Both cytokines and TGF-β have already been experimentally targeted for cancer immunotherapy. Once immune cells enter the TME, numerous mechanisms have been identifed to elicit resistance to anticancer immunity, including cancer cell intrinsic factors, immune cells and the immunosuppressive milieu. As discussed above, through immunoediting and selection pressure from anti-cancer immunity, cancer cells with loss or decrease of antigen presentation can survive anti-cancer immunity and proliferate to become resistant cancers. Upregulation of immunosuppressive signaling pathways, such as PD-1, PD-L1, LAG-3 and TIM-3, infltration of immunosuppressive cells, such as Treg cells, MDSC, M2 macrophages, a hypoxic and acidic environment, or metabolic alterations in the tumor microenvironment, have all been found to negatively contribute to anti-cancer immunity. Currently, the FDA-approved ICBs target the immune cell priming and activation (anti-CTLA4 antibody) or the fnal negative regulation of T efector cells (anti PD-1 and anti-PD-L1 antibodies). As these inhibitors only afect one to two steps of the anti-cancer immunity pathway, it is not surprising that only a minority (around 20%) of patients achieve cancer response with single agents. Slightly higher response rates have been observed with anti-CTLA4 and anti-PD1/PD-L1 combination treatments, at the cost of higher immune-mediated toxicities. Combination therapies are currently being extensively explored to target multiple defects along the immunity cycle and cancer intrinsic alterations and improve the anti-cancer efcacy, which will be covered in the following sections[5,6].

Combinations of chemotherapy and immunotherapy

Most chemotherapeutic agents were developed through its direct cytotoxic efects without consideration of the efects on immune system. Te interplay between chemotherapy and immunotherapy has been demonstrated in mouse models where mice with intact immune systems had signifcantly improved tumor resanthracyclines.To date, multiple studies have demonstrated the contribution of cytotoxic chemotherapy to anti-cancer immunity, leading to several FDA-approved combination therapies with immunotherapy[7] .

Mechanisms of action

Immunogenic cell death (ICD)

ICD is a form of regulated cell death that is amenable to activating the adaptive immune response in immunocompetent hosts. Numerous studies have shown that cytotoxic chemotherapy induces ICD and potentiates immunotherapy . Insult of cancer cells by cytotoxic chemotherapy leads to release and relocation of damageassociated molecular patterns (DAMPs) that increase the adjuvanticity of cancer cells . Release of intracellular molecules, such as ATP, enhances the recruitment of APCs; cytoplasmic annexin A1 released from cancer cells interacts with formyl peptide receptor 1 to promote interaction of dendritic cells and damaged cancer cells; exposure of endoplasmic reticulum chaperone proteins, such as heat shock protein 70 (HSP70), HSP90 and calreticulin, promotes the phagocytosis of stressed cancer cells by dendritic cells; cytosolic DNA and RNA stimulate the secretion of type I interferon and other proinfammatory cytokines through the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway, toll-like receptor 3 (TLR3) and TLR9; Type I interferon and other molecules released by stressed cancer cells, such as high mobility group box 1 (HMGB1), promote dendritic cell maturation and antigen presentation to T cells; and C–C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligannd

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1 (CXCL1) and CXCL10 facilitate T-cell recruitment.

Increase in antigenicity of cancer cells While ample evidence exists that chemotherapy increases the adjuvanticity of cancer cells through ICD, less is known about enhancement of antigenicity by chemotherapy. Many of the commonly used cytotoxic agents, such as anthracyclines, cyclophosphamide, platinum and taxanes, target cell cycle progression in proliferating cells and induce apoptosis. After tumor cell death, antigen-presenting cells engulf dying tumor cells and present tumor neoantigens to immune cells. In addition, several other studies show that cytotoxic agents upregulate antigen-presenting machinery. Gemcitabine can signifcantly upregulate the expression of human leukocyte antigen (HLA)-A, B and C through increased expression of β2-microglobulin and alter the peptide antigen repertoire expressed on HLA class I. A similar phenomenon is also observed with topotecan which upregulates HLA class I expression through activation of NF-κB/Interferon-β/MHC-I signaling axis. As discussed above, ICD and stimulation of the cGAS/ STING pathway induces type I interferon productionthe molecular drivers afect multiple steps along the cancer-immunity cycle[8,9]

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Modulation of gene expression

In addition to the cytotoxic chemotherapy, another major class of small

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molecular drugs are epigenetic modulators. Epigenetic modulation, such as DNA methylation, histone modifcation, chromatin remodeling and the readout of these modifcations, has tremendous impact during oncogenesis and is a critical event in some cancers, such as loss of tumor suppressor genes from DNA methylation. Hence, epigenetic modulators constitute an ever-expanding class of anti-neoplasm agents. In addition to direct induction of ICD and stimulation of antitumor immunity, as seen with histone deacetylase (HDAC) inhibitors vorinostat and panobinostat , another major contributing mechanism to the synergy between epigenetic modulators and immunotherapy is through gene expression modifcation. Both HDAC and DNA methyltransferase (DNMT) inhibitors have been shown to upregulate the antigen processing and presentation machinery. Both HLA class molecules and tumor-associated antigens have been found to be upregulated by epigenetic modulators. Epigenetic modulators also have direct impacts on the immune system to potentiate anti-cancer immunity. Tey can upregulate co-stimulatory molecules, such as CD80, CD86 and ICAM-1, and immune checkpoints CTLA4, PD1 and PD-L1 . Furthermore, cytokines can also be induced, and response to immunotherapy can be augmented by epigenetic modulators. Te innate immune system can be modifed by epigenetic modulators as well. Activating receptor NKG2D on the surface of NK cells and stressing-inducing ligand MICA and MICB on tumor cells can all be induced by HDAC inhibitors to increase NK cell killing of tumor cells[13] .

Detrimental efects of chemotherapy on immunotherapy

One of the major detrimental efects of chemotherapy to the immune system is lymphodepletion which can be immunosuppressive. In fact, some of the immunosuppressive drugs used in clinic to treat autoimmune diseases are cytotoxic chemotherapy used for cancer treatment, but with diferent doses Detrimental efects of chemotherapy on immunotherapy One of the major detrimental efects of chemotherapy to the immune system is lymphodepletion which can be immunosuppressive. In fact, some of the immunosuppressive drugs used in clinic to treat autoimmune diseases are cytotoxic chemotherapy used for cancer treatment, but with diferent doses and schedules. It is still controversial whether lymphodepletion induced by chemotherapy is suppressive for anti-cancer immunity. Lymphodepletion associated with cancer chemotherapyand schedules. It is still controversial whether lymphodepletion induced by chemotherapy is suppressive for anti-cancer immunity. Lymphodepletion associated with cancer chemotherapy

Potentiation of anti-cancer immunity by radiation

Both antigenicity and adjuvanticity are critical for immune response. RT can augment both antigenicity and adjuvanticity in addition to alteration of the local TME. RT increases tumor antigenicity through multiple pathways. First, similar to chemotherapy as discussed above, radiation can induce MHC-I expression and enhance tumor antigen presentation. Second, radiation induces ICD. During ICD, annexin A1 guides antigen-presenting cells to dying cancer cells while HSP70, HSP90, HMGB1 and other molecules promote uptake and cancer antigen presentation to T cells. It has been shown that radiation induces translocation of calreticulin to the plasma membrane, and release of HMGB1. Tird, radiation downregulates CD47 expression on the cell surface and enhances the cancer cells' uptake and antigen presentation . CD47 presents as a "do not eat me" signal to APCs and is overexpressed in many cancer cells. Fourth, reactive oxygen species (ROS) generated during ionizing radiation can modify macromolecules, such as proteins and DNA, and increase antigenicity. In addition to direct DNA damage, the presence of oxygen and generation of ROS are critical for radiation induced tissue injury. Another important contribution of radiation to anticancer immunity is increased adjuvanticity. Radiationinduced DNA damage and cytoplasmic leakage of DNA from micronuclei activate the innate and adaptive immune response via cGAS/STING pathway and upregulate the expression of type I interferon pathway. Tis pathway is critical for radiation induced anti-cancer immunity. Silencing of cGAS in bone marrow-derived dendritic cells impairs T cell priming. In addition to nuclear DNA, mitochondrial DNA breaks also have a role in activating a type I interferon response and synergizing with nuclear DNA breaks .In addition to the cGAS-STING pathway, ICD, release of DAMPs and cytokines can enhance adjuvanticity, elicit migration of pro-anti-cancer immune subpopulation, decrease immunosuppressive cells, alter TME and tilt

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immune response to cancer cell killing. Overall, radiation converts cancer cells as an in situ vaccine to elicit anticancer immunity. Inhibition of anti-cancer immunity by radiation In contrast to what is discussed above, ample evidence also exists that radiation induces an immunosuppressive TME. In addition to cancer cells, radiation can kill normal cells, including immune cells, especially when broad feld radiation is considered. Furthermore, radiation can alter the TME and, instead of tilting to anti-cancer immunity, induce an immunosuppressive milieu. Several studies showed that radiation induces infltration and aggregation of MDSCs, which contributes to the immunosuppressive TME through multiple pathways. Te same STING pathway that contributes to the cancer adjuvanticity at least partially contributes to the aggregation of MDSCs in tumor tissues . In addition, radiation can promote the expression of TGF-β and TGF-β family activin A, thus promoting the recruitment of Treg cells and reducing the infltration of CD8+T cells. TGF-β is upregulated upon radiation . In a preclinical study, TGF-β neutralization and radiation increase T cell priming and decrease tumor growth and metastasis. Other mechanisms of the immunosuppressive efects of radiation include the dysregulation of tumor blood vessels, hypoxia , stroma , tumor-associated macrophages (TAMs) , cancer-associated fbroblasts (CAFs) , cytokines and so on. Moreover, the abnormal expression of these components is also related to radiation resistance. In conclusion, the formation of an immunosuppressive TME by radiation is complicated process and targeting these immunosuppressive elements provides a new direction for enhancing RT-induced anti-tumor immunity[14,15,16].

Potential mechanisms

Direct efect on immune cells

Many of the aberrant signaling activities have profound impacts on immune cells. Te VEGF-VEGFR pathway plays critical roles in almost every subpopulation of immune cells. VEGFRs are expressed on activated and memory T cells. Engagement of VEGF-VEGFR leads to activation of the downstream signaling pathways in T cells, inhibits TCR (T cell receptor)-dependent activation in T cells and suppresses the cytotoxic activity of T cells . In Treg cells, VEGFR2 is selectively expressed in FOXP3high Treg cells. Besides Treg cells, VEGF can activate JAK2 and STAT3 and induce accumulation of Gr1+CD11b+MDSCs. In dendritic cells, production of VEGF by human tumors inhibits dendritic cell maturation through the NF-kappa B pathway. Increased plasma VEGF levels are associated with increased number of immature dendritic cells, and surgical removal of tumors partially reverses these efects .In applying these preclinical fndings to clinical trials, the combination of angiogenesis inhibitors and ICB signifcantly improved the treatment outcomes in metastatic renal cell carcinoma and has gained several FDA approvals. Similar direct efects on immune cells are also seen with many other targeted agents already approved by the FDA or in development. For example, ibrutinib is FDA approved for chronic lymphocytic leukemia/lymphoma (CLL), mantle cell lymphoma, marginal zone lymphoma and Waldenström's macroglobulinemia. It modulates T cells by inhibiting Bruton's tyrosine kinase (BTK) and IL2-inducible T cell kinase (ITK), and drives a T1-selective pressure in T lymphocytes and a preferential inhibition of T2 response. In patients with CLL, it markedly increases CD4+and CD8+T cell numbers, decreases Treg/CD4+T cell ratio, downregulates immunosuppressive CD200 and CD272 expression and decreases the production of immunosuppressive IL-10 production. Currently, seven clinical trials are ongoing to combine ibrutinib with immune checkpoint inhibitors for treatment of cancer[17].

II. SUMMARY

IO is a fundamentally different approach to cancer therapy and is redefining the way that both solid and haematological tumours are treated. However, this new treatment paradigm is still in its infancy, and there is a long way to go in optimising the use of these novel therapies, minimising their toxicities and learning how to integrate them into the current standard of care. Furthermore, given their high cost, there are challenges ahead in incorporating them into healthcare systems in an economically sustainable manner, while increasing availability for patients. ICPis have been the focus of the recent revolution in IO, with two main antibodies (i.e. pembrolizumab and ipilimumab) receiving multiple approvals for PD-1/PD-L1 and CTLA-4 blockade, respectively. Owing to their success, there has been significant interest in combining IO agents with conventional therapies. However, despite their promising efficacy in the clinic, the ICPis produce significant toxicities in some patients. These adverse effects are frequent, but different from those seen with conventional

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cancer therapies. Therefore, clinical research is beginning to focus on managing and predicting these toxicities, and monitoring long-term outcomes. This should lead to guidelines on how to manage these new therapies and should encourage clinicians to use them as early as possible in treatment pathways. While the pipeline of ICPis is ever-expanding, the introduction of cancer vaccines and CAR-T cell therapies is also rapidly growing. In particular, there is a strong emphasis on developing new IO agents that can modulate T-cell activity through signalling pathways (e.g. VEGF-A, LAG-3 and IDO-1), with a view to increasing understanding of how modulation of these pathways can restore the body's natural ability to fight cancer. The investigation of new targets and pathways in the IO area is vital to developing new therapies; however, it is important to note that combinations of presently approved IO agents with existing chemotherapeutic or biological agents are also generating significant interest.

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