# Comparison and Synergy of iVAC and CRISPR-Related Tumor Immune Strategies: Value Reassessment Under A Zero Genome Risk Reference

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**Abstract.** Intratumoral vaccine chimera (iVAC) is a protein level immune activation strategy that co delivers PD-L1 degrading agents and exogenous antigen peptides to tumor cell lysosomes through covalent nanobodies. It can complete antigen cross presentation while degrading PD-L1, and no off target mutations were observed in the detection as it does not involve genome editing. This article takes this as a zero-genome-risk reference and systematically compares existing data on iVAC and CRISPR tumor immune strategies from three dimensions: safety, persistence, and targeting depth. The results showed that the CRISPR strategy has accumulated preliminary clinical evidence in targeting intracellular driven mutations and long-term effectiveness of single editing (BRL-201 has a four-year complete response rate of 85.7% and an estimated five-year progression free survival rate of 40.6%), and off target detection methods continue to improve (TOPO seq found topology induced off target, and base edited NK cell products have obtained clinical approval); IVAC relies on pre stored CMV memory T cells, with transient modifications and a lack of long-term data. The existing evidence suggests that the two strategies may complement each other rather than replace each other in terms of security features, persistence, and depth of action. In the future, it is necessary to accumulate long-term human data on iVAC, promote the validation of CRISPR editing tools in solid tumors, and conduct clinical exploration of prospective combination therapies.

**Keywords:** Intratumoral vaccine chimeras; iVAC; CRISPR; Tumor vaccine; gene editing.

## 1. Introduction

Tumor immunotherapy has made breakthrough progress in the past decade, with strategies such as Immune Checkpoint Inhibitors (ICIs), Chimeric Antigen Receptor T-cell therapy, and tumor vaccines entering clinical practice [1,2]. However, issues such as low immune response to "cold" tumors, difficulty in infiltrating solid tumors, and significant individual differences in neoantigens still need to be addressed [3,4].

In 2026, the Chen Peng research group at Peking University reported in Nature the intratumoral vaccine chimera (iVAC), which utilizes covalent nanobodies to co deliver PD-L1 (Programmed Death Ligand 1) degrader and CMV derived exogenous antigen peptide to lysosomes, completing antigen cross presentation while degrading PD-L1 and activating pre-existing virus specific memory T cells [5]. In the mouse model, iVAC achieved complete tumor regression and re challenge resistance, and no off target mutations were observed in the detection due to the absence of genome editing throughout the process [5]. This strategy provides a zero genomic risk possibility for the field of tumor vaccines. At the same time, CRISPR-Cas9 gene editing technology has accumulated certain clinical data in tumor vaccine related fields such as CAR-T by directly modifying the genomes of immune cells or tumor cells [6,7]. The emergence of iVAC makes it necessary to re-examine the actual performance of CRISPR strategy in terms of safety, persistence, and targeting depth.

This article aims to systematically compare the research progress of iVAC and CRISPR related tumor immune strategies from the three core dimensions of safety, persistence, and targeting depth,

analyze the possible synergistic relationship between the two strategies, and cautiously and objectively reassess the application value of CRISPR strategies in the field of tumor immunity.

## 2. The Basic Mechanism and Possible Limitations of iVAC

The mechanism of action of iVAC includes targeted binding, lysosomal degradation, and antigen presentation. Firstly, the covalently engineered nanobodies at the end of iVAC molecules specifically recognize and bind to PD-L1 on the surface of tumor cells, forming stable covalent complexes; Subsequently, the complex enters the cell through endocytosis and is transported via the endosome lysosome pathway. PD-L1 is gradually degraded in the acidic environment of lysosomes, and the inhibitory effect of tumor cells on T cells is subsequently relieved; At the same time, the exogenous antigen peptides carried by iVAC are cleaved by proteasomes and cross presented through endogenous MHC class I molecules (Major Histocompatibility Complex class I), displaying "viral markers" on the surface of tumor cells and activating pre-existing virus specific memory T cells, thereby transforming immune "cold" tumors into "hot" tumors [5]. The cleverness of this strategy lies in its clever utilization of the abundant antiviral immune memory resources in the adult body - it is estimated that over 60% of adults carry CMV specific memory T cells - thus breaking through the traditional tumor vaccine's dependence on tumor self neoantigens [5].

In mouse model experiments, researchers inoculated colon cancer cells expressing humanized PD-L1 into mice and subsequently administered iVAC treatment. The results showed that the complete tumor regression rate of the iVAC treatment group reached 100%, and the regression mice exhibited strong resistance in the tumor re challenge experiment, suggesting that iVAC can induce persistent anti-tumor immune memory [5]. In the patient derived breast cancer like organ model, iVAC using CMV derived antigen also showed significant T cell activation ability and tumor killing effect [5]. These preclinical data fully demonstrate the feasibility of iVAC as a novel tumor immune strategy.

However, the efficacy of iVAC is highly dependent on the reserve of T cells in the body that can be reactivated. When patients experience significant T cell exhaustion due to long-term tumor burden or previous treatment, the immune resources that iVAC can mobilize will be greatly reduced [8]. T cell exhaustion manifests as loss of effector function, decreased proliferation ability, and epigenetic reprogramming, which are common bottlenecks that constrain the efficacy of various immunotherapies [8]. Therefore, for patient populations with severely insufficient T cell reserves, the applicability of iVAC may be limited.

In addition, the antigen presentation process of iVAC still cannot completely avoid MHC restriction issues. There are significant differences in the HLA subtypes carried by different patients, and the presentation efficiency and immunogenicity of the same antigen peptide may vary greatly in different individuals [3]. Taking CMV derived antigens as an example, although the virus has a high infection rate in the population, there are individual differences in the binding affinity of specific antigen epitopes to different HLA molecules, which means that a fixed antigen module is difficult to cover all populations. In contrast, personalized neoantigen vaccines have significant advantages in matching accuracy by screening the optimal tumor specific antigen for each patient through high-throughput sequencing and bioinformatics prediction [3]. However, their preparation cycle is long, the cost is high, and clinical promotion faces practical obstacles.

From the perspective of persistence, the immune remodeling brought by iVAC is essentially temporary. It can push tumor cells to a state that is easily recognized by the immune system in a short period of time, but this state is not recorded in the genome and is not transmitted to tumor offspring cells during cell division. As exogenous iVAC molecules are gradually degraded and cleared, their immune activation effect may gradually weaken [5]. At present, relevant research has not provided follow-up data with a sufficiently long time span to clarify the specific duration for which this immune surveillance effect can be maintained. This feature is in sharp contrast to CRISPR mediated genome editing, which, once completed, can stably inherit its modification effects through cell division and theoretically have more lasting therapeutic benefits.

Finally, although iVAC effectively reshapes the tumor immune microenvironment at the protein level, it cannot directly intervene in the fundamental genetic abnormalities that drive tumor occurrence and development. For tumors dominated by driver mutations such as KRAS and TP53, relying solely on protein level immune remodeling often fails to reach the root of the disease, which is also an important reason why CRISPR based strategies still have irreplaceable value in targeting depth [9].

## 3. Three Comparative Dimensions of CRISPR Related Strategies

### 3.1. Security

The safety controversy surrounding CRISPR-Cas9 technology has been ongoing since its inception, with a core concern being off target effects - Cas9 nucleases may introduce DNA double strand breaks at unexpected genomic sites, leading to chromosomal translocations, deletions, and even carcinogenic mutations [6]. This is also an important background for the introduction of iVAC as a zero genome risk strategy into the comparative framework. However, in recent years, research on off target mechanisms has progressed from simple sequence similarity analysis to more complex chromatin structure levels, and people's understanding of off target risks has also deepened.

In 2025, Duan et al. used TOPO seq technology to systematically reveal for the first time the effect of DNA topology on abnormal activation of Cas9 and base editors [10]. Research has found that the negative supercoiled state of DNA can significantly alter the cutting activity of Cas9, and some off target sites induced by topological structure can even withstand high levels of sequence mismatch without being recognized by traditional sequence alignment tools [10]. This means that early methods that relied solely on the similarity between gRNA and target sequences to assess off target risks had systematic blind spots and may have overlooked sites with real safety hazards. TOPO seq advances off target assessment from sequence recognition level to chromatin physical state level, providing a new technical dimension for CRISPR safety evaluation [10].

At the level of translational applications, CRISPR safety optimization is advancing synchronously in two directions: tool accuracy and expression regulation. In 2026, a study jointly published by Zhu Shiguo's team and Huang Xingxu's team at Shanghai University of Traditional Chinese Medicine showed that precise modification of TIGIT genes on the surface of NK cells using base editing technology can reshape the CD155 signaling pathway and significantly enhance the anti-tumor activity of NK cells [11]. This study adopts single base editing instead of traditional double strand break strategy to minimize genomic perturbations, reflecting a trend towards higher precision. At the same time, a study in 2025 inserted therapeutic payloads into endogenous regulatory sites such as NR4A2 and RGS16 that are biased towards local expression in tumors, limiting the expression of effector molecules to the tumor microenvironment and reducing systemic toxicity to normal tissues [12]. These developments indicate that the safety issues of CRISPR are not stagnant but are gradually improving through continuous technological iterations.

However, when compared to iVAC, the CRISPR strategy still cannot completely overcome the inherent concerns brought about by rewriting at the genomic level. The target of iVAC is clearly limited to PD-L1 protein and exogenous antigen peptides and does not involve any changes in DNA sequence. Its potential risks mainly focus on non-specific activation of protein degradation pathways or insufficient immunogenicity of antigen peptides within a controllable range [5]. Even after optimization, CRISPR is still essentially a direct intervention in genetic information, and long-term safety data - especially genetic stability across the cell division cycle - still requires more comprehensive clinical validation.

### 3.2. Durability

The intervention process of iVAC has the characteristics of being rapid and direct and can reshape the tumor immune microenvironment in the short term after a single administration. However, as mentioned earlier, this remodeling is temporary and not accompanied by permanent changes to the

genome. If future clinical studies find that iVAC requires repeated administration to maintain therapeutic efficacy, then treatment frequency, economic cost, and patient compliance will become practical obstacles in practical applications. Especially for advanced cancer patients, frequent intratumoral injections not only increase the difficulty of operation but also may bring risks of complications such as infection and bleeding.

In contrast, once CRISPR mediated genome modification is completed, its effects typically have stronger persistence. Taking BRL-201 developed by Bangyao Biotechnology as an example, this product is a CAR-T cell therapy based on a non viral site integration platform. It uses CRISPR technology to accurately insert the CAR gene into the PD1 site, achieving stable expression of CAR while blocking the PD-1/PD-L1 (Programmed Death-1/Programmed Death-Ligand 1) inhibition pathway [13]. The long-term follow-up data from the IIT clinical study, presented at the 67th Annual Meeting of the American Society of Hematology (ASH) in 2025, showed that as of July 11, 2025, 21 patients with relapsed/refractory B-cell non Hodgkin's lymphoma who received BRL-201 treatment had a median progression free survival (mPFS) of 20.4 months, an overall objective response rate (ORR) of 100%, a complete response rate (CR) of 85.7%, and the world's first patient to receive treatment had a cancer free survival of over 5 years [13]. These data demonstrate the potential of CRISPR engineered cell therapy in persistent control at the clinical level.

It should be pointed out that BRL-201 is essentially a CAR-T cell product, rather than a strictly defined tumor vaccine, and is therefore more suitable as a clinical reference for CRISPR persistence features, rather than a one-to-one horizontal comparison with iVAC. But the differences between the two still have important implications: if one strategy relies on repeated administration to maintain effectiveness, while the other strategy has the opportunity to achieve longer-term therapeutic benefits through a one-time intervention, their positioning in clinical applications will be clearly distinguished - iVAC may be more suitable for local treatment scenarios that require rapid immune activation, while CRISPR strategy is more suitable for systemic interventions that pursue long-term disease control.

### 3.3. Targeted Depth

The core advantage of iVAC lies in its rapid immune remodeling at the protein level, which can efficiently relieve the immunosuppressive state of tumor cells and activate bystander T cells with exogenous antigens. However, this intervention does not address the upstream driving factors of tumor occurrence and development. For tumor types dominated by specific gene mutations, such as KRAS mutant pancreatic cancer or TP53 mutant triple negative breast cancer, it is often difficult to achieve fundamental disease control by simply relying on immune environment modification at the protein level [9].

The unique value of CRISPR technology lies precisely in its ability to deeply advance interventions to the genomic level. In 2025, T-knife Therapeutics developed TK-6302, a TCR-T cell therapy targeting PRAME, which integrates multiple innovative designs such as high affinity TCR, co stimulatory CD8 co receptors, and FAS based checkpoint converters. PRAME is highly expressed in various solid tumors and extremely low expressed in normal tissues, making it an ideal tumor associated with antigen target. In November 2025, T-knife officially submitted a clinical trial application (CTA) for TK-6302, with plans to launch ATLAS Phase I clinical trials in 2026 [14,15]. This case represents a typical path for CRISPR engineered cell therapy to expand into the field of solid tumors: using gene editing technology to construct effector cells with deep targeting capabilities around well-defined tumor antigens, achieving precise targeting of tumor cells.

In terms of genetic editing targeting tumor cells themselves, Liu et al.'s study in 2025 utilized NanoCRISPR scaffolds to knock out the HO-1 gene, which alters the tolerance of tumor cells to reactive oxygen species, enhances their immunogenicity, and brings tumor cells closer to a "self vaccine" state [16]. HO-1 (heme oxygenase-1) is an important intracellular antioxidant defense enzyme, and tumor cells with high expression of HO-1 can resist oxidative stress-induced immunogenic cell death. Through NanoCRISPR scaffold mediated HO-1 knockout, the survival ability of tumor cells under reactive oxygen species attack decreases, while releasing more damage

associated molecular patterns (DAMPs), activating the antigen presentation function of dendritic cells, and initiating systemic anti-tumor immune response [16].

This type of research shares similarities with iVAC in terms of therapeutic goals - both aim to increase the likelihood of tumors being recognized by the immune system - but the implementation pathways are completely different: the former relies on heritable gene knockout methods, while the latter relies on protein degradation and antigen delivery methods. There are significant differences between the two methods in terms of risk composition and persistence of action: the HO-1 knockout effect of NanoCRISPR can persist with tumor cell division, but it needs to face long-term safety tests of gene editing; The protein level intervention of iVAC is safer and more controllable, but its effectiveness is limited. This difference precisely indicates that the two types of strategies are not simply substitutes but provide different trade-offs between targeting depth and security.

## 4. Possible Synergy between Two Strategies

Simply viewing iVAC and CRISPR strategies as interchangeable is an overly one-sided understanding. A more reasonable framework is that the two are located at different stages of the tumor immune intervention chain and can complement and collaborate in specific application scenarios. Previous literature reviews have indicated that cancer vaccines and adoptive cell therapy have potential synergistic applications in promoting antigen expansion and enhancing host immune involvement [3]. Ma et al.'s research further confirmed at the mechanistic level that vaccine enhanced CAR-T cells can synergize with the host immune system, overcoming the escape risk caused by tumor antigen heterogeneity through epitope spreading mechanisms [17]. Based on the above theoretical foundation, existing research proposes two specific joint application paths.

The first pathway is applicable to tumor types where immune exhaustion is more pronounced. In this scenario, CRISPR technology or engineered cell therapy can be used to improve the functional status of effector cells, such as enhancing T cell proliferation and cytokine secretion levels through base editing or endowing them with stronger tumor infiltration ability through CAR-T modification. Then, iVAC can be used to enhance antigen presentation in situ in tumors, providing more effective recognition signals and activation stimuli for these functionally enhanced effector cells. This "empowerment first, activation later" strategy theoretically can break through the limitations of T cell exhaustion on the efficacy of iVAC, while also compensating for the shortcomings of simple cell therapy in antigen presentation. However, the key challenges of this approach lie in timing and toxicity control: the interval time, dosage ratio, and potential cumulative toxicity between CRISPR modified cells and iVAC administration need to be clarified through rigorous preclinical studies.

The second pathway is applicable to typical immune "cold" tumors. These types of tumors typically lack sufficient endogenous antigen presentation, have sparse immune cell infiltration, and exhibit poor response to existing ICIs. In this scenario, iVAC can be used to improve the local immune environment of the tumor, pushing the previously "cold" tumor that is not prone to immune response to a stronger "hot" state - by degrading PD-L1 to relieve immune suppression, recruiting virus specific memory T cells through exogenous antigen presentation, and reshaping the cytokine profile and immune cell composition in the tumor microenvironment. Subsequently, engineered effector cells (such as CRISPR optimized TCR-T or CAR-T) will be introduced, which will face a more suitable combat environment: weakened immune suppression signals, enhanced antigen presentation, and preliminary opening of effector cell infiltration channels. In theory, this strategy of "preheating first, tackling later" can significantly improve the infiltration efficiency and killing effectiveness of subsequent cell therapy.

It should be emphasized that the above two joint paths are currently mostly at the stage of mechanism deduction and theoretical conception. IVAC itself is still in the preclinical research stage, and its long-term safety, pharmacokinetic characteristics in humans, and optimal dosing regimen are not yet clear; Although there are some clinical data on CRISPR engineered cell therapy, there have been no experimental reports on its combination with iVAC. Therefore, the clinical translational

potential of these ideas still needs to be gradually confirmed through systematic preclinical studies, including toxicity assessment of combination therapy, exploration of optimal timing, and efficacy verification.

## 5. Discussion

After systematically reviewing existing research evidence, our understanding of iVAC and CRISPR has deepened. From a safety perspective, CRISPR strategies still face comparative pressure from iVAC. Although TOPO seq and other studies have promoted a deeper understanding of off target mechanisms from the sequence level to the topological level, and technologies such as base editing and site-specific integration are constantly optimizing accuracy, systematic long-term clinical safety data is still limited [10,11,12]. The zero genomic risk feature of iVAC theoretically has clear safety advantages, but this advantage needs to be further validated in future clinical trials - after all, "not involving DNA editing" does not mean "absolutely risk-free", and safety issues such as non-specific disturbances in protein degradation pathways and potential autoimmune reactions to exogenous antigens also require long-term observation [5].

From the perspectives of persistence and targeting depth, CRISPR strategy still retains the application space that iVAC is temporarily unable to replace. The 5-year long-term follow-up data of BRL-201 has preliminarily demonstrated the persistent control potential of CRISPR engineered cell therapy in hematological tumors [13]; TK-6302 and other TCR-T therapies targeting solid tumors are advancing clinical translation, with the potential to extend the targeted depth advantage of gene editing to a wider range of tumor types [14,15]; NanoCRISPR mediated gene knockout in tumor cells provides a heritable modification method to enhance tumor immunogenicity [16]. These advances indicate that the research investment of CRISPR technology in the field of tumor immunity still has sufficient scientific basis.

It should be noted that the current comparative studies on iVAC and CRISPR strategies are not based on completely consistent levels of evidence. At present, iVAC mainly relies on preclinical research results published in 2026, and its long-term safety, applicable population range, and stable efficacy in different tumor types all need to be continuously supplemented by subsequent research [5]. However, some CRISPR related research advances, such as the long-term follow-up data of BRL-201 from conference abstracts [13] and the preclinical data of TK-6302 from publicly available materials in enterprises [14], differ in the completeness of evidence and the rigor of peer review. Therefore, a more appropriate way of expression at this stage is to acknowledge that this is a comparison at the trend level, rather than a conclusion based on the same level of evidence. The so-called 'zero genomic risk' emphasizes the technical feature that iVAC does not directly modify DNA and does not mean that it has completed comprehensive validation of long-term clinical safety.

Taking into account various factors, it is not accurate to simply place iVAC and CRISPR strategies within the evaluation framework of 'who replaces whom'. The two methods are more suitable for understanding, representing rapid immune remodeling at the protein level and persistent intervention at the genomic level, respectively. They may have their own applicable scenarios under different patient and tumor backgrounds. The question that is truly worth exploring in the future may not be which method will completely replace another, but how to choose optimal monotherapy or combination therapy in specific clinical contexts, such as tumor type, immune status, past treatment history, economic accessibility, etc.

In addition, with the rapid development of new immune strategies such as mRNA vaccine technology, oncolytic viruses, and bispecific antibodies, the toolbox for tumor immunotherapy is continuously enriched. The comparison between iVAC and CRISPR should not be conducted in isolation but should be examined within the broader context of technological evolution. The combination, sequencing, and synergy between different strategies may become one of the core directions for future research on tumor immunotherapy.

## 6. Conclusion

As a zero genomic risk tumor immune strategy, iVAC achieves in situ reprogramming of tumor cells to antigen-presenting cell like states through covalent nanobody mediated PD-L1 degradation and cross presentation of exogenous antigens, demonstrating significant anti-tumor activity and immune memory induction ability in preclinical models. This article is based on iVAC as a safety reference, systematically comparing its differences with CRISPR related tumor immune strategies from three dimensions: safety, persistence, and targeting depth. The potential synergistic relationship between the two strategies is analyzed, and the application value of CRISPR strategies is cautiously reassessed.

The research results indicate that in terms of safety, the zero genomic risk feature of iVAC poses comparative pressure on CRISPR strategies, but CRISPR technology has made substantial progress in understanding off target mechanisms, optimizing editing accuracy, and regulating expression; In terms of persistence, the temporary remodeling of iVAC complements the heritable modification of CRISPR, with the former being suitable for rapid immune activation and the latter being more suitable for long-term disease control; In terms of targeting depth, iVAC excels at reshaping the immune microenvironment at the protein level, while CRISPR can directly intervene in tumor driver genes, and there are significant differences between the two at the intervention level.

The two types of strategies are not substitutes but represent the technological choices at different stages of the tumor immune intervention chain. Future research directions should focus on clarifying the pharmacokinetics and long-term safety of iVAC in the human body; Accumulate systematic clinical data on CRISPR strategies in solid tumors. Only by fully understanding their respective advantages and limitations can we achieve precise selection and reasonable combination of tumor immunotherapy strategies, ultimately bringing greater clinical benefits to patients.

## Authors Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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