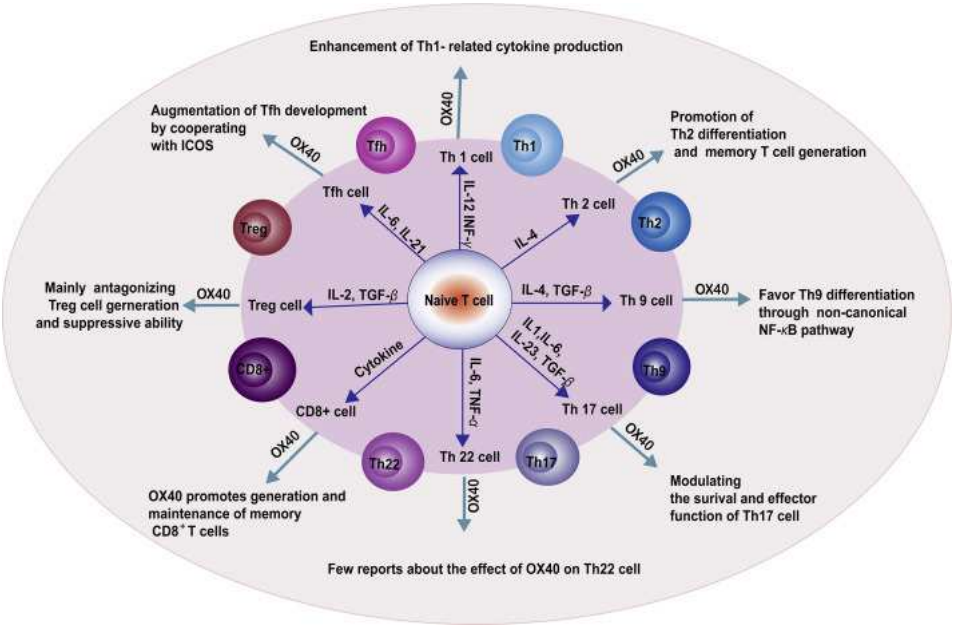
Hot Immunotherapy Target: OX40

Introduction

OX40 is a crucial T-cell co-stimulatory molecule that mediates the survival and expansion of CD4+ and CD8+ T cells in various animal models of infection, cancer, and autoimmunity. It regulates memory T-cell responses and is a popular target in the field of innovative drugs. OX40 agonists were once highly regarded in the anti-tumor field, attracting significant interest from pharmaceutical companies. However, issues related to efficacy and side effects have hindered progress, with no agonists having advanced beyond Phase 2 clinical trials. Recently, OX40 inhibitors have shown promising results in clinical studies in the autoimmune field. On June 27, 2023, Sanofi announced that Amlitelimab successfully completed a Phase 2b clinical trial for the treatment of moderate-to-severe atopic dermatitis, making it the second OX40 inhibitor to pass Phase 2 trials after Rocatinlimab. Therefore, OX40 remains a highly translatable and promising drug target that warrants further research.

The Highly Anticipated "Accelerator" of the Immune System

OX40 (CD134) is a member of the tumor necrosis factor receptor (TNFR) superfamily and serves as an essential T-cell co-stimulatory molecule. It is primarily expressed on activated CD4+ and CD8+ T cells and plays a critical role in regulating immune responses, promoting T-cell proliferation, and ensuring T-cell survival. Its ligand, OX40L (CD252), is expressed on various antigen-presenting cells (APCs) such as B cells, dendritic cells, and macrophages. Upon antigen stimulation, APCs present the antigen to T cells, activating them. Subsequently, OX40 on the T-cell surface binds to its ligand OX40L, initiating downstream signaling that prolongs the survival of activated T cells. This signaling pathway has two main immunomodulatory effects: first, it enhances the proliferation and survival of non-regulatory effector T cells, promoting the secretion of inflammatory cytokines such as IL-2, IL-4, IL-5, and IFN-γ; second, it inhibits the function of regulatory T (Treg) cells, reducing the expression levels of Foxp3 and CD25.



By targeting OX40 with antibodies to either activate or inhibit its activity, the intensity of the

immune response of T cells to antigens can be modulated. Currently, global research on OX40 is primarily focused on two major areas: oncology and autoimmunity.

Setbacks in the Oncology Field

In cancer treatment, early clinical studies indicated that OX40 agonists might enhance tumor immune responses by promoting the activation and memory formation of effector T cells. Since 2009, patents for OX40 agonists have increased annually, peaking in 2018 and 2019. At that time, having an OX40 agonist in the pipeline was standard for major international pharmaceutical companies, and domestic companies also joined the research. Unfortunately, since 2019, the development of OX40 agonists in the oncology field has faced continuous setbacks. Pfizer was the first to terminate the development of its OX40 agonist PF-04518600 due to a low objective response rate of only 5.8% in Phase 1 clinical trials, with most patients showing no response. Subsequently, other companies such as Roche, Bristol-Myers Squibb, GSK, and AstraZeneca also terminated their OX40 agonist programs due to disappointing efficacy. Monotherapy response rates for OX40 agonists did not exceed 10%, and combination therapy results were also mediocre. The core issue lies in the complexity of immune system regulation and the direct impact of OX40 on the immune system. High agonist activity can trigger cytokine release syndrome, posing a life-threatening risk. Companies, concerned about safety, limited agonist activity and adopted low-activity, high-dose strategies that failed to meet clinical endpoints. Despite substantial efforts in dosing methods and sequences, most attempts ended in failure. Thus, the road to anti-cancer therapy with OX40 agonists remains long and challenging.

Promising Advances in the Autoimmunity Field

While the oncology field has faced significant challenges in developing OX40-targeted therapies, the autoimmune field has seen promising progress. The application of OX40 in autoimmune diseases began relatively late, with only two OX40 inhibitors, Rocatinlimab and Amlitelimab, entering clinical trials in 2019. Rocatinlimab is used to treat adult patients with moderate-to-severe atopic dermatitis. It selectively reduces activated OX40+ T cells, inhibits T-cell proliferation, and reduces the production of inflammatory cytokines. Phase 2 clinical trial data showed that the proportion of patients with ≥75% improvement in EASI from baseline at week 16 was higher than in the placebo group, with efficacy comparable to the star drug dupilumab for atopic dermatitis. This development pipeline has been acquired by Amgen at a high price and is currently in Phase 3 clinical trials. Amlitelimab, on the other hand, restores immune system homeostasis by targeting OX40L to block T-cell activation. It was acquired by Sanofi during Phase 1 clinical trials and successfully completed Phase 2b clinical trials for the treatment of moderate-to-severe atopic dermatitis. The successive successes of Rocatinlimab and Amlitelimab suggest that the field of OX40 inhibitors might experience renewed interest, attracting companies like Inmagene and Henlius to enter the fray. While the oncology field faces setbacks, the autoimmune field is full of hope, reflecting the charm of innovative drug development amidst uncertainty.

Functional Antibodies Offer Numerous Advantages in OX40 Research

Functional antibodies targeting OX40 include agonistic and blocking antibodies. Agonistic antibodies bind to OX40 and activate the signaling pathway, while blocking antibodies bind to OX40L and prevent OX40 activation. Both types of antibodies have been successfully used to

study the role of OX40 in T-cell activation, proliferation, and immune memory.

Compared to the complex, costly, and time-consuming process of constructing transgenic mice, functional antibodies are more flexible and efficient for research purposes. Their advantages include:
- High specificity: They can accurately recognize and bind to OX40 without interfering with other receptors or pathways, ensuring that results accurately reflect the function of the signaling pathway.
- Direct modulation of OX40 signaling: Agonistic antibodies can mimic natural ligand activation signals to study their effects on T cells, while blocking antibodies can inhibit the interaction between OX40 and its ligand to study negative regulatory effects.
- Strong controllability: By adjusting dosage and timing, researchers can precisely control signal activation or inhibition, facilitating the exploration of effects at different times and intensities.
- Wide applicability: They can be used in in vitro cell experiments, animal models, and clinical studies, making the results more generalizable and translatable. They can also be used in combination with other therapeutic methods to study synergistic effects, which is significant for developing combination therapies.

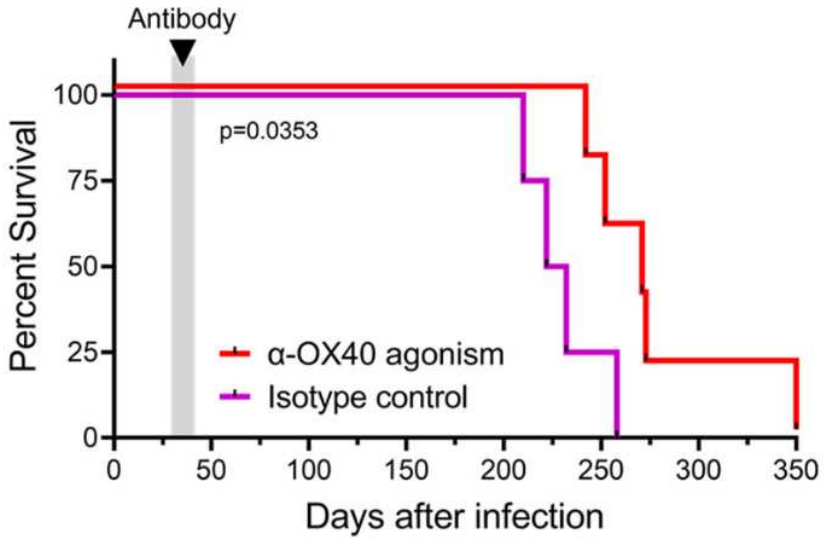
In summary, functional antibodies, with their high specificity, direct modulation, strong controllability, and wide applicability, help in-depth exploration of OX40 signaling and its potential therapeutic applications.

Bio X Cell offers a series of antibodies that are 0.2μm filter-sterilized, low in endotoxins, and free of azide compounds, suitable for various functional experiments.

Product Application Cases:

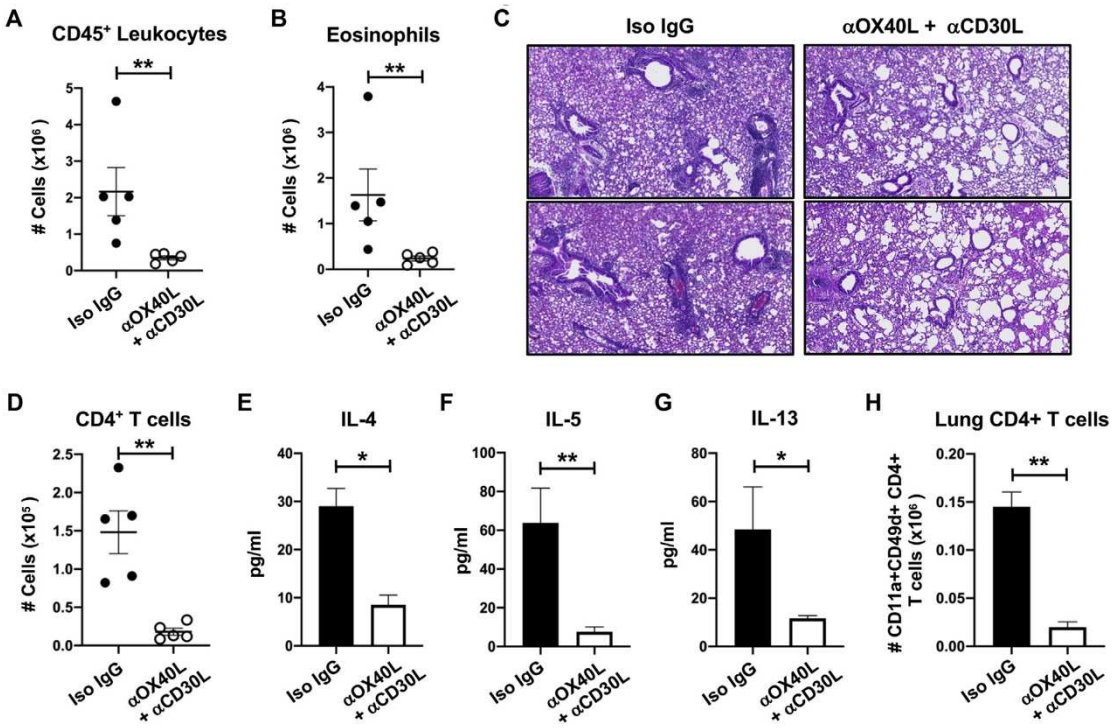
OX40 Agonist: InVivoMAb anti-mouse OX40 (CD134)

The InVivoMAb anti-mouse OX40 (CD134) from Bio X Cell has been cited in at least 36 publications and has demonstrated good in vivo effects. For example, in a study by Abigai et al., Bio X Cell's OX40 agonist was used. In this study, wild-type C57BL/6 mice were injected with 100 μg of the α-OX40 agonist (OX-86, Cat#BE0031), α-PD-1 (29 F.1A12, Cat#BE0273) blocker, or isotype control antibody (HRPN, Cat#BE0088) four weeks after Mycobacterium tuberculosis infection, twice a week for two weeks. The mice were then monitored for survival. They found that treatment with the OX40 agonistic antibody extended the long-term survival of mice infected with Mycobacterium tuberculosis and significantly reduced lung bacterial load, outperforming PD-1 blockade therapy.



OX40 Inhibitor: InVivoMAb anti-mouse OX40L (CD134L)

A study published in The Journal of Allergy and Clinical Immunology demonstrated that the combined blockade of OX40L and CD30L signals can inhibit allergen-driven memory cell responses and lung inflammation, offering a new strategy for treating allergic diseases. In this study, researchers established a mouse HDM (house dust mite) allergy model. Mice were sensitized either intraperitoneally or intranasally; intraperitoneal sensitization was performed on day 0 using 20 μg of HDM extract mixed with 2 mg of alum, while intranasal sensitization involved administering different doses of HDM on corresponding days. After the formation of immune memory, nasal allergen challenge was conducted. On the first and third days of secondary allergen challenge, mice were injected intraperitoneally with 250 μg of OX40L antibody (RM134L, BioXCell) and 250 μg of CD30L antibody (RM153, BioXCell) or 500 μg of control Rat IgG (BioXCell). The authors then analyzed the effects of combined antibody treatment on the disease model using bronchoalveolar lavage fluid (BALF) analysis, lung histology, and ELISA.



The combined blockade of OX40L and CD30L effectively inhibited allergen-driven memory cell responses and lung inflammation. WT mice were sensitized intranasally with HDM on days 0, 1, and 2. From days 14 to 17, mice received intranasal HDM challenge and were treated with OX40L and CD30L antibodies. The following were observed: (A, B) the number of CD45+ cells in the BALF, (C) H&E staining of lung tissue sections, (D-G) the number of CD4+ T cells in the BALF, and the levels of IL-4 (E), IL-5 (F), and IL-13 (G). (H) The number of CD11a+CD49d+CD44hiCD4+ T cells in the lungs.

References:

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Author: Bio X Cell