agenusnews

Vol. 4 · Issue 12 · June 17, 2021

Fc-Enhancement is Critical for the Optimal Performance of Antibodies

Antibody design is a crucial aspect in creating therapies that enable cancer killing and in turn bring the most benefit to patients. The primary function of the antibody is to bind to a target antigen; they can also be specifically designed for immune effector functions through their Fc (fragment crystallizable) region.

Although antibodies naturally have a specific structure, they can be modified using innovative engineering approaches to optimize both their binding and function. The Fc region of monoclonal antibodies can be changed to improve their therapeutic effect. The importance of the Fc region has been a hot topic of debate in I-O. Some have pursued antibodies that nullify the Fc regions, others maintain the natural structure, or enhance the Fc regions.

At Agenus, our scientists discovered that modifying the Fc region of certain antibodies in specific ways can unlock novel biology and optimize their functionality and anti-tumor response. In 2018, we published in the journal Cancer Cell, data showing that "enhancing" the Fc region of antibodies targeting CTLA-4 or TIGIT improves their tumor fighting abilities. In contrast, antibodies targeting PD-1 show optimal function with an inactive Fc region.

Since then, we have continued to deepen our understanding of antibody engineering and biology to design our next generation molecules with this novel technology. The function of the Fc region is an important component to the immune response against cancer, and by enhancing it, we can improve and optimize an antibodies' therapeutic potential. **In today's newsletter, we outline some of the critical functions and how this Fc-enhanced design can lead to an optimally performing antibody.**

Antibody Biology – Why Fc-Enhance?

Antibodies are Y-shaped molecules made of organized links of proteins joined together. By design, antibodies have two binding sites, the variable region or 'front-end' that bind to targets on cancer cells or immune cells and an Fc region that can bind to specialized Fc receptor-expressing immune cells **(see figure 1)**.

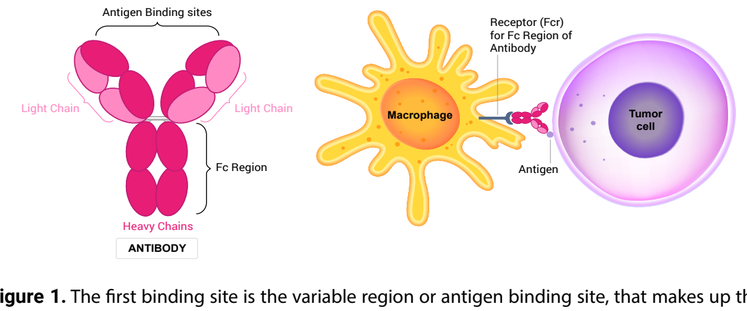

Figure 1. The first binding site is the variable region or antigen binding site, that makes up the 2 small arms of the "Y". This site of the antibody binds to its target of interest. Second is the Fc region, which makes up the stem or tail of the" Y". This region binds to Fc receptors on various immune cells.

When antibodies are fully bound, they elicit a range of functions that enable their therapeutic activity. The Fc region is critical to this because it can anchor the antibody to an immune cell and activate additional immune functions. **Many of these anti-cancer functions of antibodies can be fine-tuned by optimizing the interaction of the Fc region with the receptors they bind to on immune cell populations.**

Fc-enhanced means that the Fc region of the antibody has been engineered to increase its interaction with other immune cells. Enhancing this region allows antibodies, like anti-CTLA-4 or anti-TIGIT, to act as a glue between a T cell and an antigen presenting cell, which creates a stable immune synapse for an optimal immune response. When bound, the Fc region in turn activates T cell response by promoting a strong connection between the T cells and the Fc receptor expressing antigen-presenting cells or natural killer (NK) cells. Furthermore, enhanced Fc-signaling can further activate additional immune cells and dendritic cells to further improve its cancer killing ability. **Therefore, we Fc enhance our antibodies - to make the activity of the antibody as a whole stronger and to unlock novel biology.**

Fc-Enhancing Can Lead to Multiple Outcomes that Improve the Immune Response Against Cancer

Improved Cancer Cell Killing Abilities:

Many of the anti-cancer activities of antibodies require interactions between the Fc region and its Fc receptor on immune cells. These interactions help enable the body's immune cells to eliminate cancer. With Fc-enhanced antibodies, we can improve these cancer killing processes and in turn, may enable more optimal responses to treatment.

Antibody-dependent cell-mediated cytotoxicity (ADCC) is a critical mechanism underlying the clinical efficacy of therapeutic anticancer antibodies, which is mediated in large part through the Fc region. In ADCC, antibodies first recognize the cancer by binding to the target on the cancer cells. Then, the Fc region of the antibody engages Fcγ receptor-expressing immune cells (in this case, NK cells). This Fc-engagement then triggers the NK cell to kill the cancer cells via ADCC. **The Fc region is critical to this activity, because its engagement with the NK cell is what enables this process to occur.**

In addition to directly eliminating cancer cells, ADCC can also be used to eradicate highly immune suppressive regulatory T cells (Tregs) in the tumor microenvironment. For example, CTLA-4-expressing Tregs that infiltrate the tumor suppress anti-tumor immunity, whereas eliminating these Tregs promotes tumor eradication by other immune cells, such as CD8 T cells. **The reality is that unmodified antibodies lack the ability to promote efficient ADCC due to suboptimal binding to Fc receptors.** By enhancing the Fc region of our antibodies, we improve the interaction between the antibody and the Fc receptor expressing NK cell, which can result in improved cell killing or Treg depletion, as we expect our next generation anti-CTLA-4 therapy AGEN1181 to perform.

Another anti-cancer process where an enhanced Fc region can improve the therapeutic activity is in antibody-dependent cellular phagocytosis (ADCP). **In ADCP, antibodies bound to target cancer cells activate the Fc receptors on macrophages through their Fc region.** This activation induces phagocytosis, resulting in internalization and degradation of the target cancer cell through the macrophage "eating" the tumor cell. Again, this process is mediated by the engagement of the Fc region of the antibody, which can be further optimized though an Fc-enhanced design.

These Fc receptor-dependent antibody functions are important components of the immune response against cancer. Through our deep science we have uncovered the criticality of this region in promoting an optimal immune response, and strategically designed some of our key agents with an enhanced Fc region to maximize its therapeutic potential. This improves the antibody's cancer killing mechanisms, leading to a more optimally performing agent.

Potential to Broaden the Therapeutic Reach:

One of the most important characteristics of our Fc-enhanced design is the potential ability to treat a broader patient population than conventional antibody approaches.

People naturally express polymorphic variants of Fcy receptors which have different abilities to bind to the Fc region of antibodies. These polymorphic variants can be described as high affinity or low affinity Fcy receptors. **Unmodified antibodies, (i.e with a standard Fc backbone) have a low-binding affinity for the low affinity variant and do not effectively trigger anti-cancer activities.** Therefore, patients with the low affinity variant may have a sub-optimal response to therapy. Engineering the Fc region can improve antibody binding for these patients, which can create a more optimal therapeutic effect.

I**n other words, Fc enhancing our antibodies enables them to potentially broaden their therapeutic benefit even to people who have alterations or polymorphisms.** Our approach allows our antibodies to potentially benefit a significantly larger patient population, regardless of Fcy receptor allele status.

We have seen evidence of this in the clinic, with our Fc-enhanced anti-CTLA-4 antibody AGEN1181. **AGEN1181 respondes to date include patients with less favorable genetic characteristics, such as the low affinity FcyRIIIA allele.** Yervoy does not typically benefit patients expressing the low affinity allele; which constitute ~40% of the population. That means up to 40% of the population may not be receiving optimal benefit from an unmodified anti-CTLA-4 antibody. AGEN1181, through Fc-engineering, may be able to address this gap and expand benefit to both high and low affinity patient populations. The Fc-enhanced design of AGEN1181 is critical in potentially extending the benefit of CTLA-4 blockade to more patients.

At Agenus, we strive to create innovative therapies that stem from our deep understanding of cancer biology and immunology. Using our deep science, we've employed innovative approaches, like Fc-enhancement, to optimize the performance of our antibodies. Our teams are constantly interrogating the immune response against cancer to find new opportunities for therapies, new technologies for improved discovery, and to develop our next innovations.

References:

1. Somparyac L. How the immune system works, Sixth edition.
2. Waight JD et al., Cancer Cell. 2018 Jun 11; 33(6): 1033–1047.e5
3. Antibody Drug Conjugates J. Mar 2019.
4. Nigro C et al., Ann Transl Med. 2019. 7(5).
5. https://www.sinobiological.com/research/complement-system/cdc
6. Kamen L et al., J of Immuno Methods. 2019.