agenusnews

Vol. 4 · Issue 5 · March 9, 2021

Novel Immune Tools Tutorial:TIGIT, iNKTs, CTLA-4

In this issue of agenusnews, we are providing additional insights into some of the most exciting immuno-oncology next generation targets, TIGIT, and our back to the future view on CTLA-4. Inhibiting these molecules aims to release the cloaking effect tumors have over the immune system and here we discuss one type of immune protagonist: iNKT cells. Scientists from leading academic institutions worldwide have established TIGIT, CTLA-4, and iNKT cells as being central to normal tissue homeostasis and control, and how cancers can subvert these signaling pathways and grow. Following the solid scientific foundations that took years to establish, we are now prepared to take development risk, aiming ultimately to extend quality and quantity of life for patients worldwide.

CTLA-4: one of the immune system "brakes"

CTLA-4 is a critically important pathway for immunotherapy. The first checkpoint inhibitor ever approved was an anti-CTLA-4. This pathway plays a key role in how cancer escapes the body's immune system. **CTLA-4 is a protein found on the surface of T cells and enables the growth of cancer by putting the "brakes" on any immune attack against cancer cells.** When CTLA-4 is bound to proteins on antigen presenting cells (eg. CD80, CD86), it inhibits the many functions of T cells. Therefore, blocking this binding aims to restore the immune response and remove the immune "brake". The binding of anti-CTLA-4 antibodies permits T cells to remain activated and continue their tumor killing response.

Thus far, anti-CTLA-4 therapy has been complicated by significant adverse events such as inflammation of the large bowel (colitis), inflammation of the lungs (pneumonitis) and other toxicities. These can be debilitating and sometimes lasting. There are rarer toxicities too, such as neuroendocrine effects involving the pituitary gland which can affect ~10% of patients treated with ipilimumab. Our next-generation anti-CTLA-4 antibody, AGEN1181, has been Fc-enhanced with structural changes to achieve optimal activity and improved safety. We were the first to show that Fc-enhancement improves the therapeutic index with fewer side effects. Interestingly, we have shown that our anti-CTLA-4 antibody decreases the levels of regulatory T cells, which serve to inhibit an immune response inside a tumor mass.

We are now seeing the importance of targeting this pathway and features of Fc-enhancement being validated in the clinic. AGEN1181 has demonstrated activity in difficult to treat tumors, with 6 total confirmed objective clinical responses in colon, ovarian, and endometrial cancers in early phase 1 trials without any significant toxicity.

TIGIT: critical receptor on immune cells

Like PD-1 and CTLA-4, TIGIT is one of the major players in our immune system. **TIGIT is a receptor expressed on the surface of immune cells, such as T, NK (natural killer cells), and regulatory T cells.** TIGIT inhibits both innate and adaptive immune responses against cancer by preventing the tumor killing actions of these cells. When TIGIT binds to PVR (a protein expressed on cancer cells), the ability of T and NK cells to fight cancer is weakened: cancers can grow and metastasize. **By blocking TIGIT/PVR binding, it may be possible to restore the anti-tumor response of these immune cells, making it an attractive therapeutic option.**

Given the success of anti-CTLA-4 and anti-PD-1 therapies, clinicians have been enthusiastic about the potential of immunotherapies, as they are showing better results than chemotherapy. But, there has been a long wait for additional promising immunotherapy targets that would benefit patients; TIGIT is now emerging as one such option. However, first generation TIGIT molecules have demonstrated limitations in the clinic.

AGEN1777 is our TIGIT bispecific candidate designed to deliver best-in-class performance. It is Fc-enhanced to deliver improved activity even as monotherapy. For example, we have seen preclinical data supporting use as monotherapy in anti-PD1 refractory setting where patients have tumors growing on anti-PD1. The bispecific format co-targets another immune receptor we have not yet disclosed that addresses an escape mechanism from anti-TIGIT therapy. These key features may address the weaknesses of current first generation anti-TIGIT antibodies. We plan to initiate a Phase 1 study of AGEN1777 later this year.

iNKTs: the body's natural intelligent cells

The immune system has a variety of different cell types, each with special functions. **Invariant natural killer cells (iNKTs) are "intelligent" immune cells. These are like the special forces of the immune system with a broad range of abilities.** iNKTs cells harness both the innate and adaptive immune system to fight disease. We call these "intelligent cells" because of their ability to navigate to the site of trouble, examine the situation there, and based on their situational analysis develop and implement an action plan. As their name implies, iNKT cells have some features of natural killer cells (a key component of innate immunity) and some features of T cells (a key component of adaptive immunity). iNKTs can direct themselves to the site of the problem, which could be cancer or infectious diseases, for example. These cells work to kickstart the immune response and can do so rapidly, as they respond quicker in the presence of inflammation.

In contrast to "regular" T cells, iNKT cells naturally conduct surveillance of tissues and can leave the blood stream and enter tumors without requiring prior activation: iNKT cells naturally travel to tumor tissues and home to this microenvironment, using their specific homing receptors. iNKTs can detect tumor cells through their invariant T cell receptor (iTCR) that binds to CD1d (a target on some tumor cells and many tumor-supporting cells of the "tumor microenvironment"). iNKTs can also respond to tumor stress ligands through NKG2D. They then elicit direct tumor killing through the release of cytotoxic granules, as well as recruiting other immune cells via cytokines. **iNKTs can also recruit T and NK cells to attack tumor cells, creating an immune cascade that can control cancers via multiple mechanisms.** Another unique feature of iNKTs is their ability to elicit a broad range of activities. These cells can promote both proinflammatory and regulatory immune responses.

Our iNKT cell therapy is allogeneic: we have developed and industrialized ways to harvest healthy iNKT cells from donors, increase their numbers in bioreactors, and then infuse these iNKT "soldiers" into other patients who desperately need these reinforcements to fight cancer, COVID-19, or other threats. These cells are intrinsic defenders and can be used "off-the-shelf" without requiring genetic manipulation. They are designed to treat patients affordably and accessibly.

Through our subsidiary, AgenTus Therapeutics, we are currently advancing our iNKTs as treatment for patients with moderate to severe symptoms of COVID-19. The rationale for our COVID-19 trial is covered in an earlier newsletter. Our Phase 1 trial in cancer is expected to begin in the second quarter of 2021.

These are some of the many ways the immune system can fight cancer. We are committed to creating innovative, disruptive therapies that harness the immune system to control disease. By doing so, we are bringing new hope to patients and getting closer to finding cures. We look forward to giving deeper insights into our exciting emerging medicines based on world-class science and drug development in future newsletter issues.