Equillium, Inc.
www.equilliumbio.com

Restoring immune balance: Targeting CD6 to treat autoimmune and inflammatory disease

Equillium's itolizumab downregulates T effector cell activity and trafficking to tissues. It is currently being tested against acute graft-vs-host disease (aGVHD), lupus nephritis, and uncontrolled asthma.

The immune system is a powerful internal force safeguarding against attacks from pathogens. In autoimmune diseases, this force damages, rather than protects. Effector T cells (T_{eff}) can drive autoimmunity and tissue damage unless their activity is balanced by anti-inflammatory regulatory T cells (T_{reg}). A T cell receptor believed to be central to this balance is CD6. Equillium, Inc. is pioneering an anti-CD6 antibody product candidate, itolizumab, as a novel therapy to treat multiple autoimmune and inflammatory diseases. Because CD6 is highly expressed on T_{eff} but not T_{reg} cells, itolizumab selectively downregulates these pro-inflammatory cells, restoring immune balance (Fig. 1).

Itolizumab is being tested in clinical trials in acute graft-vs-host disease (aGVHD), lupus nephritis, and uncontrolled asthma. A key advantage of itolizumab is its unique, multi-modal, disease-modifying mechanism. Because itolizumab acts upstream of pro-inflammatory cytokines, it may have greater potential than therapies targeting single cytokines to shut down runaway immune responses.

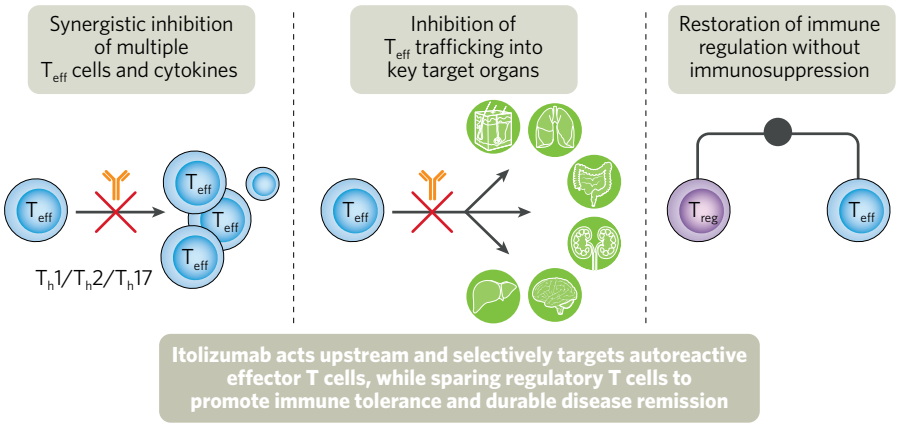

Fig. 1 | Itolizumab anti-CD6 inhibitor in autoimmunity. Multi-modal activity against pathogenic T effector cells.

Inhibiting the CD6-ALCAM pathway

A subset of T_{eff} cells, Th17 cells, express high levels of CD6, are often steroid insensitive, and are implicated in a range of autoimmune diseases, including psoriasis, inflammatory bowel disease, multiple sclerosis, and GVHD. ALCAM (Activated Leukocyte Cell Adhesion Molecule), the CD6 counter-ligand, is expressed on antigen presenting cells and some endothelial and epithelial cells. CD6-ALCAM interaction is required for the formation of a functional immune synapse, optimal T cell activity (activation, proliferation and differentiation) and trafficking.

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Engagement of the CD6-ALCAM pathway is associated with increased pro-inflammatory cytokine secretion, including interferon-gamma, tumor necrosis factor alpha, interleukin 6 and interleukin 17. CD6 and ALCAM are elevated in disease settings involving inflammation of the skin, gut, lung and kidney, with tissue-infiltrating T_{eff} cells expressing high levels of CD6 and the inflamed organs overexpressing ALCAM. In preclinical models, knock-out experiments demonstrate that T cell activation, inflammatory cytokine production, and trafficking into tissues are significantly reduced in the absence of CD6. Anti-CD6 monoclonal antibodies have been shown to attenuate autoimmune and allergic inflammation in multiple models of disease. Inhibiting the CD6-ALCAM pathway with itolizumab is believed to selectively inhibit T_{eff} cell activation and trafficking into tissues, while sparing T_{regs}, which has the potential to promote immune tolerance and induce durable disease remission.

Clinical validation

In 2013, itolizumab received approval in India as a safe and effective treatment for plaque psoriasis. In aGVHD, steroid-insensitive CD6-high T cells contribute to gastrointestinal inflammation, a key driver of mortality. Equillium is currently testing itolizumab in a US phase 1b/2 trial (EQUATE) in patients with high-risk aGVHD, who typically have low response to steroids, the current standard of care. Granted both Orphan and Fast Track status for aGVHD by the US Food and Drug Administration, if approved, itolizumab will fill a need for a first-line therapy for aGVHD. Positive interim data from the EQUATE trial showed an 80% overall response rate (ORR) across the first three dose cohorts and complete responses (CR) in 7 of 8 patients responding. In the second two dose cohorts, the ORR was 100%. Responses have been rapid, with most patients achieving a CR within 15 days, and durable, as patients in the first two dose cohorts maintained responses through day 57. This data suggests opportunities to expand the potential therapeutic application of itolizumab for patients with chronic GVHD and as a potential preventative treatment for patients who have undergone hematopoietic stem cell transplantation

Equillium also has ongoing phase 1b trials in systemic lupus erythematosus/lupus nephritis (EQUALIZE), for which itolizumab was granted Fast Track designation, and uncontrolled asthma (EQUIP). Although T_{eff} cells are known to play a central role in both indications, they are complex, heterogenous diseases where multiple pro-inflammatory cytokines contribute to disease pathogenesis. Studies have shown the CD6-ALCAM pathway is overactive in the inflamed kidney and lungs of these patients. The potential of itolizumab to inhibit activation of multiple pro-inflammatory pathways, as well as the infiltration of T_{eff} cells into tissues, could be a significant advantage in treating these serious diseases.

Equillium is developing itolizumab, its novel first-in-class immune-modulating therapeutic, with a mission to dramatically improve the lives of patients with severe autoimmune and inflammatory disorders.

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