Subburaj et al used targeted metabolomic analyses that quantitatively measure the concentrations of a predefined set of metabolites that were previously identified. The data presented here support a prospective, longitudinal validation study in an independent pediatric patient cohort with the goal of combining potential metabolic biomarker panels with immune cellular and cytokine markers to obtain a biomarker algorithm for accurate risk assignment before onset and diagnosis of cGVHD. The authors must be congratulated for embarking on this important and very large project and should consider further collaborations, including adding an adult patient cohort.

Because of the inherent sensitivity of metabolomics, subtle alterations in biological pathways can be detected and can provide novel insights into pathophysiologic mechanisms of diseases. Thus, metabolomics and innovative developments in informatics and analytical technologies should be investigated not only for biomarker discovery but also for increasing our understanding of cGVHD clinical phenotypes and their association with immunoregulatory pathways relevant in studying the development and persistence of cGVHD. This should allow for a more individualized treatment approach in the future, as recently suggested by the NIH consensus group.[9] Furthermore, metabolism is an attractive target for therapeutic intervention in GVHD because differentiation, proliferation, and function of innate immune cells are also subjected to metabolism-dependent regulation.[6,10] Targeting metabolism for therapy of GVHD, however, will require a thorough understanding of the unique metabolic properties and programs of the multiple cellular components involved in cGVHD.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Dhunputh et al, page 300

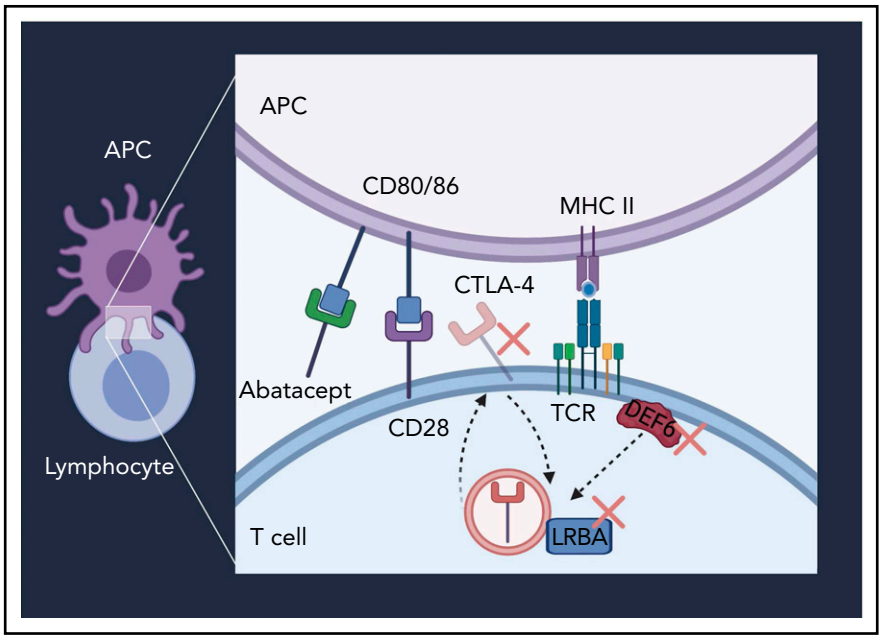
Monogenically driven therapies: the new first line

Lisa R. Forbes Satter | Baylor College of Medicine

In this issue of *Blood*, Dhunputh et al describe the efficacy of off-label use of abatacept, a CTLA-4 immunoglobulin protein, in a cohort of patients with pediatric immune-mediated cytopenia related to CTLA-4–related pathway defects (CTLA-4 deficiency, lipopolysaccharide responsive and beige-like anchor protein [LRBA] deficiency, and DEF6 deficiency).[1]

Identification of the genetic etiology of inborn errors of immunity (IEIs)[2] has revolutionized the use of precision targeted therapy to treat complications of IEIs that are unrelated to infection. Immune-mediated pathologies, such as autoimmune cytopenia (AIC), are a prominent feature of IEIs as a result of CTLA-4–related pathway defects. Severe AIC is often refractory to initial immunosuppression, and flares of disease are common. The disrupted mechanisms driving AIC include T cell– and B cell–driven autoimmunity, pathologic inflammation, poorly controlled inflammatory responses, and impaired production. Dhunputh et al focused on autoimmunity-driven AIC caused by CTLA-4–opathies. CTLA-4 is an inhibitory receptor essential for T-cell regulation. CTLA-4 regulation is key to modulating inflammation and turning down the inflammatory response by inducing sequestration of costimulatory ligands on antigen-presenting cells. Interaction with LRBA prevents its degradation. Furthermore, Serwas et al[3] discovered that interaction with DEF6 is important for CTLA-4 availability and trafficking. Defects involving *CTLA-4*,[4] *LRBA*,[5] and *DEF6*[3] result in immunodeficiency and autoimmunity (see figure).

Abatacept was first studied in tumor necrosis factor α–refractory rheumatoid arthritis[6] and was US Food and Drug Administration approved in 2007. In the study by Dhunputh et al, the authors used the drug to mechanistically target the mutant genes. Patients with CTLA-4 defects are unable to suppress $CD4^+$ proliferation compared with healthy controls, leading to a phenotype of humoral immunodeficiency and autoimmunity. A prior study showed that CD80/86 ligand–dependent proliferation was blocked by abatacept.[4] Egg et al[7] recently reported a cohort of patients treated with various immunomodulatory



CTLA-4–related defects treated with abatacept. Antigen-presenting cell (APC) and T-cell interaction with CTLA-4 pathway defects denoted with X. MHC, major histocompatibility complex; TCR, T-cell receptor.

agents for the disease manifestations of CTLA-4 deficiency and found that a majority of patients with AIC responded to abatacept. Concurrently, a long-term study of 76 patients in Europe with LRBA deficiency treated with abatacept showed improvement in most organ systems affected.[8] In this study, 9 patients with pediatric immune cytopenia were treated with abatacept for CTLA-4 deficiency (n = 5), LRBA deficiency (n = 3), and DEF6 deficiency (n = 1). At the start of treatment, 6 were in complete remission (CR) on other therapies, two had partial remission (PR), and one had not achieved remission. After starting therapy, an additional patient achieved CR, and the remaining 2 patients in this group reached sustained PR. Six patients were able to wean off all other therapies. No patient had a new flare of AIC on therapy. Abatacept response continued for up to 4.9 years after initiation of therapy and allowed for steroid-sparing therapy.

This concept of targeted therapy has shown some promise in monogenic gain-of-function diseases in the JAK/STAT signaling pathway.[9] AIC caused by lymphoproliferation and abrogation in production has either completely or partially resolved with treatment using ruxolitinib, baracitinib, or tofacitinib in STAT1 and STAT3 gain-of-function disorders.[10] More studies are needed to assess clinical efficacy in multiorgan immune dysregulation disorders allowing for 1 drug to target multiple defects. In addition, remission of AIC is a durable outcome measure to consider in future clinical trials. Currently, there is 1 safety and efficacy trial (Safety and Efficacy of Abatacept for Treating Chronic Cytopenia in Cytotoxic T-Lymphocyte Antigen 4 [CTLA4] Haploinsufficiency; registered at www.clinicaltrials.gov as #NCT03733067), which will be enrolling patients soon, and 1 observational study (New Biomarkers for Diagnosis and Follow-up of Patients With LRBA or CTLA-4 Deficiencies; registered at www.clinicaltrials.gov as #NCT04377867).

A significant number of IEIs present with immune-mediated pathology as a major feature in addition to infection. AIC is a common manifestation in these patients. Specific genetic disorders are teaching us about basic mechanisms of autoimmunity/inflammation in humans, which in turn has led to better targeted therapy. If the cellular mechanisms or genetics are known, therapy can be personalized. The use of targeted therapies to enhance efficacy warrants close study and expansion of clinical trials in IEIs.

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