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Review Article

A role for plasma cell targeting agents in immune tolerance induction in autoimmune disease and antibody responses to therapeutic proteins

A.S. Rosenberg [a,*], A.R. Pariser [b], B. Diamond [e], L. Yao [c], L.A. Turka [d], E. Lacana [a], P.S. Kishnani [f]

[a] Office of Biotechnology Products, CDER, FDA, Bldg 71/2238, 10903 New Hampshire Ave, Silver Spring, MD 20993, United States
[b] Office of Translational Sciences, CDER, FDA, United States
[c] Office of New Drugs, CDER, FDA, United States
[d] Massachusetts General Hospital East Transplantation Biology Research Center, 13th Street, Building 149-9019, Boston, MA 02129, United States
[e] Center for Autoimmune and Musculoskeletal Diseases, The Feinstein Institute for Medical Research, 350 Community Dr, Manhasset, NY 11030, United States
[f] Duke University School of Medicine, 595 Lasalle Street, GSRB 14th Floor, Room 4010, Durham, NC 27710, United States

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ABSTRACT

Antibody responses to life saving therapeutic protein products, such as enzyme replacement therapies (ERT) in the setting of lysosomal storage diseases, have nullified product efficacy and caused clinical deterioration and death despite treatment with immune-suppressive therapies. Moreover, in some autoimmune diseases, pathology is mediated by a robust antibody response to endogenous proteins such as is the case in pulmonary alveolar proteinosis, mediated by antibodies to Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF). In this work, we make the case that in such settings, when the antibody response is high titered, sustained, and refractory to immune suppressive treatments, the antibody response is mediated by long-lived plasma cells which are relatively unperturbed by immune suppressants including rituximab. However, long-lived plasma cells can be targeted by proteasome inhibitors such as bortezomib. Recent reports of successful reversal of antibody responses with bortezomib in the settings of ERT and Thrombotic Thrombocytopenic Purpura (TTP) argue that the safety and efficacy of such plasma cell targeting agents should be evaluated in larger scale clinical trials to delineate the risks and benefits of such therapies in the settings of antibody-mediated adverse effects to therapeutic proteins and autoantibody mediated pathology.

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In the past few years, there have been reports of successful reversal of antibody and autoantibody responses with the administration of the plasma cell targeted drug bortezomib. We take note of two reports in which treatment of patients with antibody mediated pathology in the settings of ERT for infantile-onset Pompe disease and TTP with bortezomib [1,2] successfully reversed the antibody and autoantibody responses, respectively, leading to significant clinical improvement. In both settings the antibody response had been sustained in the face of treatment with immune suppressive agents including rituximab, the monoclonal antibody (mAb) which targets CD20 expressing cells, thereby depleting mature and memory B cells, but not the long lived

* Corresponding author.

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plasma cells (CD20 negative) responsible for high titer and sustained antibody responses (Fig. 1).

Reviews [3,4] of the use of bortezomib or potentially, other proteasome inhibitors in autoimmune disease and antibody mediated allograft rejection, proposing its evaluation in autoimmune myasthenia gravis and SLE, further highlight the potential of therapeutics targeting long-lived auto- or allo-antibody secreting plasma cells in relevant pathologic settings (Table 1). Indeed there are a number of diseases in which auto-antibodies play a predominant role in pathophysiology such as myasthenia gravis (mediated by antibodies to post-synaptic proteins of the neuromuscular junction) [3], the anti-synthetase syndrome (mediated by antibodies against aminoacyl-tRNA synthetases) [5], pulmonary alveolar proteinosis (mediated by autoantibodies to GM-CSF) [6], and various manifestations of systemic lupus erythematosus (SLE) [7–12]. In each of these cases, successful treatment would appear to rely on eliminating or diminishing the antibody response and induction of immunologic tolerance.

In addition to the damage caused by auto-antibodies in many autoimmune conditions, antibodies formed against the neoantigens in replacement factors are well known to abrogate efficacy in the cases of Factor VIII treatment of Hemophilia A [13] and Factor IX treatment in Hemophilia B [14] and of ERTs in the setting of Lysosomal Storage Diseases (LSDs), such as infantile-onset Pompe disease [15–17], mucopolysaccharidosis types I and II and Gaucher disease [18–19]. The negative impact of antibodies on clinical outcome is clear, for example, in infantile-onset CRIM negative Pompe disease, where disease progresses rapidly and the antibody mediated loss of efficacy of ERT hastens clinical decline and death, while tolerance induction has been shown to prevent or restore the efficacy of ERT in case studies [20–21]. Additionally, the efficacy of highly effective therapeutic proteins such as TNF specific monoclonal antibodies [22], and interferon β [23] may also be compromised by anti-drug antibodies.

1. Plasma cell targeting agents

Given the considerations above, we believe that it is appropriate to investigate the safety and efficacy of plasma cell targeting agents in larger scale clinical trials that are sufficiently powered to delineate the risks and benefits of such therapies in antibody-mediated clinical conditions. Drugs used to treat multiple myeloma, a plasma cell malignancy characterized by proliferation and accumulation of abnormal plasma cells, may provide clues for drugs that could potentially be explored for plasma cell targeting. The proteasome (24) plays a major role in cell cycle progression and immune responses. The immunoproteasome, a class of proteasome mainly expressed in cells of lymphoid origin, plays an important role in antigen processing and the immune response [24,25].

1.1. Proteosome inhibitors

As noted above, the proteasome inhibitor bortezomib ameliorated high titered and sustained antibody responses to ERT in some infantile-onset Pompe disease patients [2].

In addition, bortezomib was shown to be beneficial in a number of case reports of TTP [1,26,27,28]. In the majority of nonfamilial TTP cases, autoantibodies against ADAMTS13, a metalloproteinase that cleaves vonWillebrand factor, are associated with the disease, and patients have very low or no ADAMTS13 activity. In all instances described

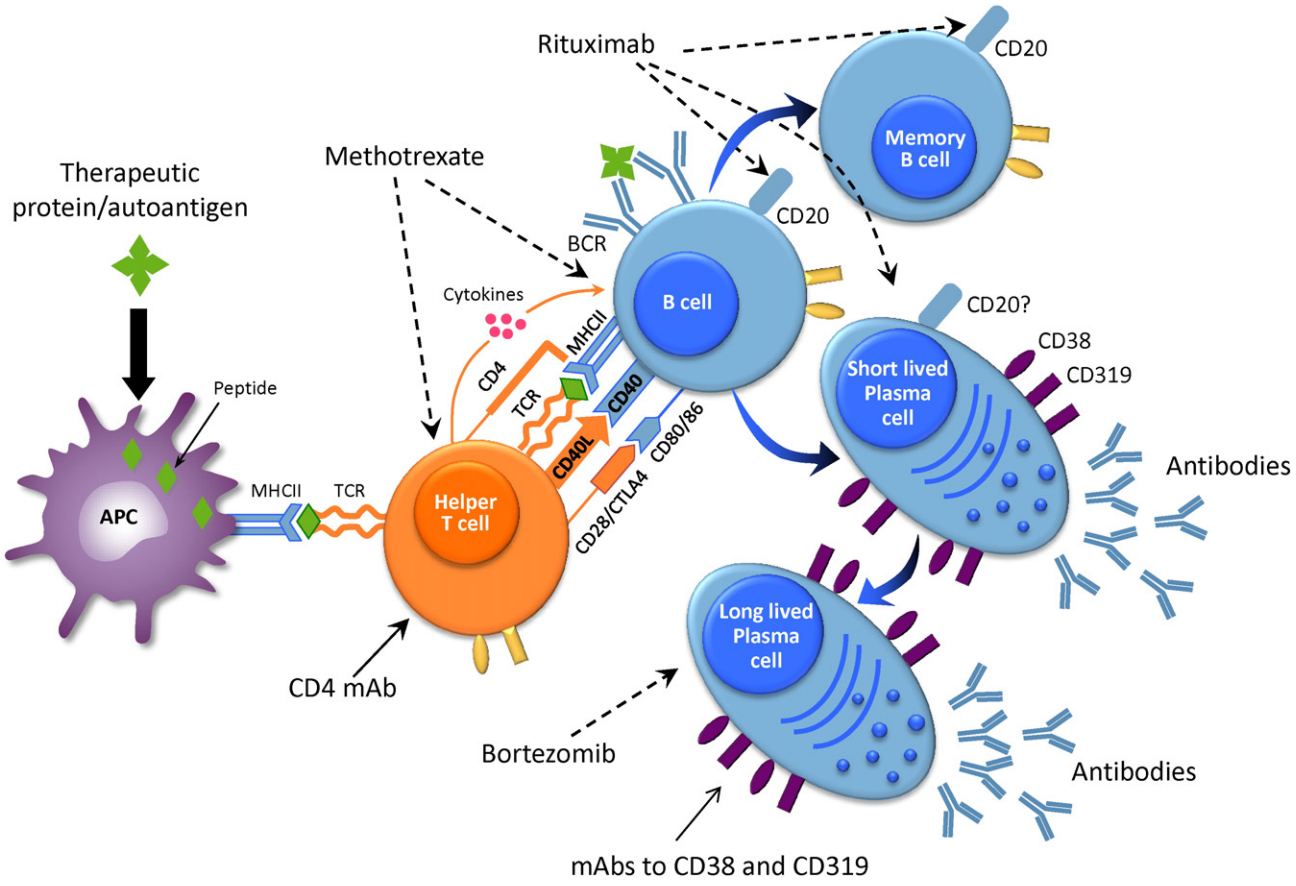

Fig. 1. Lymphocyte populations and interactions mediating antibody responses.