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Title: **New insights on what causes ITP and hope for new therapies**

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In the Aug 15 issue of the prestigious journal Blood, a relatively rare event occurred when four papers on ITP were published in one volume and I had the honour of writing an editorial on three of them. Before discussion of the three papers, however, I need to discuss some background on our immune system and the importance of a type of T cell termed a T regulatory cell (Treg).

Our immune system has many potent ways to guard us from invading infections or the development of cancer and at the same time, remarkably, is 'tolerant' of our own healthy cells or self. This self-tolerance mechanism basically works by eliminating self-reactive T and B lymphocytes in the thymus and bone marrow, respectively, when we are still developing in our moms. Like most things in nature, however, this elimination process is not absolute and some potentially self-reactive lymphocytes escape into our circulation. We all have them but while some of us develop autoimmune disease, most do not. What stops these escapees from reacting against our own tissues is due to a complicated web of peripheral immune mechanisms that keeps the bad guys in check throughout our lives. When this peripheral surveillance system fails, the self-reactive lymphocytes proliferate and react against our various tissues e.g. insulin producing beta cells in Type 1 diabetes, myelin in multiple sclerosis and in the case of ITP, our platelets. What we have learned recently is that these peripheral tolerance mechanisms are all orchestrated by a particular type of CD4+ helper T cell called a Treg. Tregs appear to be our natural immune 'magic bullet' that keeps all of our normal and abnormal immune responses in check. These regulatory cells are critical to our survival and absence of them has clearly shown the development of autoimmunity, inflammatory disorders and in some instances, even fatal consequences in both mice and humans[6].

Although defects of Tregs have been described in patients with ITP since 2006, the three papers published in Blood shed light into not only how ITP is caused, but how therapy with Rituximab works by indirectly normalizing the defective Tregs in patients. All three studies showed that patients with chronic refractory ITP have reduced numbers of Tregs and that these cells do not do their job properly. This leads to unchecked activation of self-reactive T and B cells that react against platelets leading to the eventual production of anti-platelet antibodies and cytotoxic T cells. One of the studies[1] additionally showed that, like anti-platelet antibodies, the activated T cells can move to the patient's bone marrow and potentially inhibit platelet production. The most interesting and important finding was shown by Dr Stasi's group in Rome; the B cell therapy Rituximab actually works by normalizing the Treg defect in patients with ITP and this causes a quick halt to platelet autoimmunity. There was also a fourth paper published in the volume and this was truly an added bonus. Dr Godeau's group in France showed that early Rituximab therapy in patients with ITP may have a splenectomy-sparing effect. While these exciting results still need to be confirmed in larger clinical studies, they suggest a potentially new beneficial indication for the antibody therapy.

Collectively, the importance of these papers is their suggestion that defective Tregs are at the heart of the autoimmune attack in ITP and that development of new drugs that target these cells either directly or indirectly (like Rituximab) will be the key to permanently controlling ITP.