Projekttitel: **Targeting pathogenic memory plasma cells with proteasome inhibition in chronic autoimmunity**

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Hintergrund: Pathogenic autoreactive memory plasma cells (PCs) contribute to the maintenance of autoimmunity in antibody-mediated autoimmune diseases, such as systemic lupus erythematosus (SLE) by the persistent secretion of autoantibodies. We could recently demonstrate that the proteasome inhibitor bortezomib, approved for the treatment of multiple myeloma, is clinical effective in patients with refractory systemic lupus erythematosus (SLE) by the depletion of autoreactive plasma cells (Alexander et al., ARD 2015). However, although efficiently depleted by proteasome inhibition, PCs rapidly regenerated due to B cell hyperactivity. We therefore designed a clinical trial in which bortezomib will be given on background immunosuppression in SLE (n=6) and rheumatoid arthritis (n=6) to prevent the regeneration of autoreactive PC from their precursor B cells (registered at www.clinicaltrials.gov as #NCT02102594). The aim of this project is to investigate the phenotypic and functional properties of newly generated vs. remaining PCs after proteasome inhibition with respect to cytokine production (IL-10, IL-35), origin from mucosal reactions (CCR10, IgA) and their migratory potential in correlation to clinical and serological responses. To elucidate whether newly generated PC derive from the pool of preexisting memory B cells, their specificity will be analyzed (Ig heavy/light chain repertoire).