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Next-generation Porcine Low Immunogenicity Anti-Lymphocyte Immunoglobulins shows selective depletion of T lymphocytes versus Treg and Breg.

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Polyclonal anti-lymphocyte globulins (ALG) have been used for many years in organ transplantation. Their use as induction therapy is growing, owing to their higher efficacy as compared with other induction agents. ALG, however, decrease acute rejection at a cost of increased development of BK virus, CMV and bacterial infections. In addition, as any antibody from animal origin, ALG elicit antibodies anti-N-glycolylneuraminic acid carbohydrates that contribute to formation of immune complexes to a systemic inflammation called xenosialitis and have been associated with shorter kidney graft lifespan.

To address these issues, we developed LIS1, a new generation ALG from a1,3-GT and CMAH knockout swine, lacking carbohydrate xenoantigens. Since LIS1 is obtained after immunization with human T lymphocytes and given its modified glycosylation pattern, it possibly results in different outcomes in vivo as compared with existing ALG. We therefore analyzed lymphocyte depletion by LIS1 in cynomolgus monkeys (n=13).

In macaques receiving a daily dose for 5 days of LIS1, a rapidly and significantly depletion of circulating CD8+ T cells and CD4+ T cells was recorded. Subpopulations including recent thymic emigrants, naïve, stem cell memory, central memory and RA+ effector memory T cells were significantly depleted ($p<0.002$), except for regulatory T cells that were not affected. Naive B cells, memory B cells and granzyme B+ B-reg cells were also unaffected, such as monocytes and polynuclear cells.

Taken together these results strongly suggest that LIS1 can be an attractive induction treatment with high efficacy and specificity, avoiding the deleterious side effects observed with current anti-lymphocyte/thymocyte globulins.