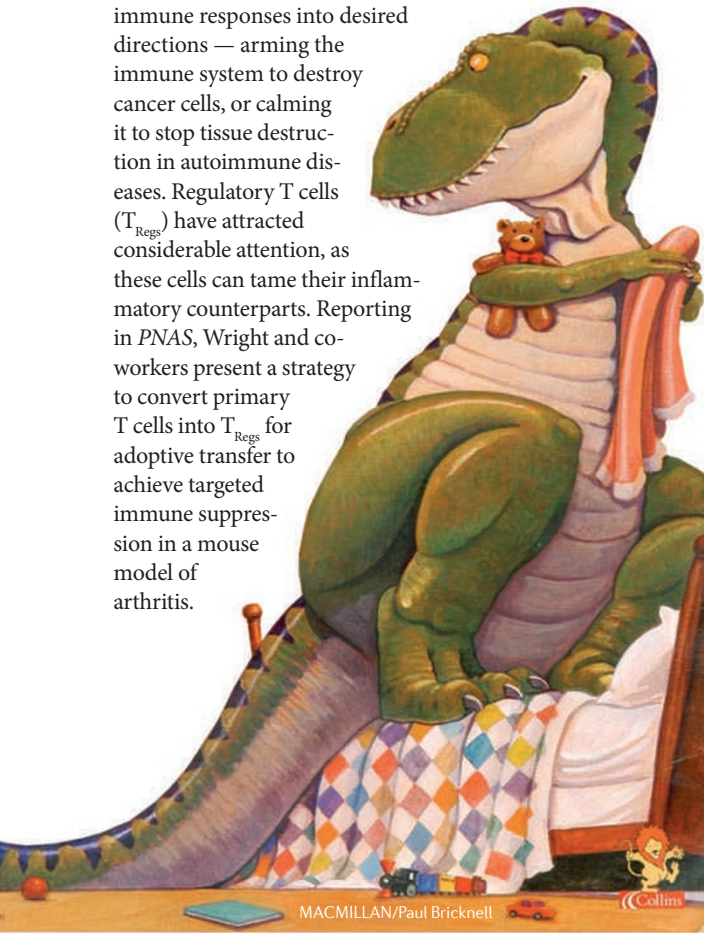
AUTOIMMUNITY

Targeted T_{Regs} tame autoimmune disease

The 'holy grail' of immunology is to find the right tools to precisely direct immune responses into desired directions — arming the immune system to destroy cancer cells, or calming it to stop tissue destruction in autoimmune diseases. Regulatory T cells (T_{Regs}) have attracted considerable attention, as these cells can tame their inflammatory counterparts. Reporting in *PNAS*, Wright and co-workers present a strategy to convert primary T cells into T_{Regs} for adoptive transfer to achieve targeted immune suppression in a mouse model of arthritis.



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The clinical translation of targeted therapy with T_{Regs} has been hampered by the fact that T_{Regs} require T cell receptor (TCR) ligation by a specific antigen to fully activate their suppressive function. Isolating and expanding antigen-specific T_{Regs} from the natural polyclonal T cell repertoire is difficult, and in autoimmune disorders the initiating antigen that is responsible for pathology is often unknown. In this study, the authors tested two strategies to engineer efficient T_{Regs} that can be 'switched on' by stimulating a retrovirally introduced TCR. The first strategy involved the insertion of an ovalbumin (OVA)-specific TCR gene construct into naturally occurring T_{Regs}, whereas the second approach involved transducing total $CD4^+$ T cells with the OVA–TCR construct and the gene encoding forkhead box protein P3 (FOXP3), a transcription factor that converts conventional $CD4^+$ T cells into T_{Regs}.

In vitro experiments showed that both strategies lead to the development of functional T_{Regs} that are capable of immune suppression, which is strongly enhanced in the presence of the OVA antigen. To test whether these cells retain their suppressive function *in vivo*, the authors used a mouse model of antigen-induced arthritis. Disease was induced by immunizing mice with methylated bovine serum albumin (mBSA) followed by intra-articular knee rechallenge with mBSA, resulting in T cell-mediated tissue damage. The engineered T_{Regs} were injected before mBSA rechallenge, and each animal received an injection of mBSA and OVA in one knee, and mBSA alone in the other (the control knee). The engineered T_{Regs} were shown to home to the OVA-injected knee and substantially decrease inflammatory knee swelling and arthritic bone destruction, while having no effect on the control knee.

Importantly, suppression occurred even though the regulatory and the pathogenic T cells recognized distinct antigens. This suggests that T_{Regs} could be engineered to express TCRs that recognize tissue-specific antigens in the target organ of autoimmune disease, thus leading to selective homing and local suppression of pathogenic T cells, irrespective of their antigen specificity. If such experiments can be translated to the human setting, it could pave the way for highly targeted T_{Reg} therapies that provide effective control of autoimmune-mediated tissue damage, without impairment of systemic immunity or the need for systemic immune suppression.

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ORIGINAL RESEARCH PAPER Wright, G. P. *et al.* Adoptive therapy with redirected primary regulatory T cells results in antigen-specific suppression of arthritis. *Proc. Natl Acad. Sci. USA* **106**, 19078–19083 (2009)