CD3-specific monoclonal antibody and was shown to cause long-term reversal of recent-onset diabetes in both mouse models. This reversal was associated with increased numbers of peptide-specific T_{Reg} cells, which were shown to produce various regulatory cytokines *in vitro* and to have a bystander effect *in vivo* that results in the suppression of heterologous autoreactive T-cell responses in the pancreas.

The combination of a systemic immunomodulator and an inducer of autoantigen-specific T_{Reg} cells has the dual advantage of reversing recent-onset type 1 diabetes and of reducing the risk of side-effects (given that the T_{Reg} cells only suppress immune responses in a site-specific manner). This combination therapy, therefore, might be a useful clinical strategy.

Davina Dadley-Moore

ORIGINAL RESEARCH PAPER Bresson, D. *et al.* Anti-CD3 and nasal proinsulin combination therapy enhances remission from recent-onset autoimmune diabetes by inducing Tregs. *J. Clin. Invest.* **116**, 1371–1381 (2006)

response was influenced by the density of the antigen and the affinity of the antigen for the BCR. Moreover, the amount of antigen that was taken up by the B cell and the subsequent ability of the B cell to present the antigen to T cells were proportional to the total amount of antigen accumulated in the central cluster.

On the basis of these observations the authors generated a computer model that reproduced the empirical data. The model showed that this antigen-collection process allows the B cells to discriminate between ligands of different affinity. So, high-affinity interactions favour further B-cell spreading and exposure to membrane-bound ligands before contraction and collection. By contrast, low-affinity interactions result in inefficient spreading and low levels of antigen collection and therefore reduced B-cell activation.

Lucy Bird

ORIGINAL RESEARCH PAPER Fleire, S. J. *et al.* B cell ligand discrimination through a spreading and contraction response. *Science* **312**, 738–741 (2006)
FURTHER READING Harnett, M. M. B cells spread and gather. *Science* **312**, 709–710 (2006)

INNATE IMMUNITY

Finding flagellin

Bacterial flagellin is a known ligand for Toll-like receptor 5 (TLR5). However, several recent papers have now revealed that in addition to the TLR5 pathway, which responds to extracellular flagellin, host macrophages can respond to cytosolic flagellin through members of the NOD-like receptor (NLR) family.

The recognition of pathogen-associated molecular patterns by host TLRs is a key component of innate immunity, and much has been learned about TLRs and their signalling pathways over the past decade. More recently, attention has turned to the role of non-TLR pattern-recognition receptors in innate immunity, including the cytoplasmic NLR family. Details of the NLR-signalling pathways are beginning to emerge, and NLRs are known to be involved in secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β) by macrophages. IL-1β is produced initially as a zymogen that is activated for secretion by caspase-1.

In *Salmonella enterica* serovar Typhimurium (*S. typhimurium*) infection, the NLR protein ICE-protease activating factor (IPAF; also known as CARD12 and CLAN) was known to be involved in caspase-1 activation and IL-1β secretion, but until now, the *S. typhimurium* ligand for IPAF was unknown. Two independent groups led by Gabriel Núñez and Alan Aderem investigated the nature of the innate immune response to *S. typhimurium* infection. Both groups confirmed that IPAF was required for IL-1β production and caspase-1 activation by macrophages. Additionally, they both found that *S. typhimurium* mutants that either lack or have mutated flagella did not stimulate caspase-1 activation or IL-1β secretion, suggesting that flagellin is the *S. typhimurium* ligand for IPAF.

As flagellin is also a known ligand for TLR5, the involvement of TLRs was examined. Both groups found that *S. typhimurium* could stimulate caspase-1 activation and IL-1β secretion by TLR5-deficient macrophages and by wild-type macrophages, and in addition, Franchi *et al.* found normal levels of caspase-1 activation and IL-1β secretion by tolerant macrophages that are refractory to TLR stimulation. Taken together, these results suggest that macrophages sense flagellin through a TLR5-independent pathway that relies on the cytoplasmic sensor IPAF.

Further confirmation that IPAF senses flagellin in the cytosol independently of TLR5 comes from the fact that both groups also demonstrated that purified flagellin delivered to the cytosol triggered caspase-1 activation in wild-type but not IPAF-deficient macrophages. The mechanism by which flagellin accesses the cytosol during infection remains to be completely elucidated. However, genetic evidence presented by Miao *et al.* suggests that it is transferred directly into the eukaryotic cytoplasm by the virulence-associated type III secretion system.

These results are echoed by results published recently in two independent papers, one in *PLoS Pathogens* and one in *The Journal of Experimental Medicine*, which indicate that an NLR is involved in cytosolic sensing of *Legionella pneumophila* flagellin through a TLR5-independent, caspase-1-dependent pathway.

Sheilagh Molloy, Senior Editor,
Nature Reviews Microbiology

ORIGINAL RESEARCH PAPERS Franchi, L. *et al.* Cytosolic flagellin requires Ipaf for activation of caspase-1 and interleukin 1β in *Salmonella*-infected macrophages. *Nature Immunol.* **7**, 576–582 (2006) | Miao, E. A. *et al.* Cytoplasmic flagellin activates caspase-1 and secretion of interleukin 1β via Ipaf. *Nature Immunol.* **7**, 569–575 (2006) | Ren, T. *et al.* Flagellin-deficient *Legionella* mutants evade caspase 1 and *Naip5*-mediated macrophage immunity. *PLoS Pathog.* **2**, e18 (2006) | Molofsky, A. B. *et al.* Cytosolic recognition of flagellin by mouse macrophages restricts *Legionella pneumophila* infection. *J. Exp. Med.* **203**, 1093–1104 (2006)