In the news

ROTAVIRUS VACCINES

About half a million children under five years of age die as a result of rotavirus infection each year. But hopes for a safe and effective vaccine have been raised by two recent studies published in *The New England Journal of Medicine* (5 January 2006).

The rotavirus vaccines Rotateq (Merck & Co.) and Rotarix (GlaxoSmithKline) reduced the number of cases of severe gastroenteritis in clinical trials by 98% and 85%, respectively. Both vaccines also markedly reduced the number of infants requiring hospital treatment for symptoms of rotavirus infection (which include dehydration and diarrhoea).

Most deaths from rotavirus occur in developing countries, but almost all children worldwide are infected with rotavirus at least once by five years of age. And each year, ~70,000 children in the United States receive hospital treatment (*USA Today*, 4 January 2006), as well as ~1 in 38 children in the United Kingdom by the age of five (*BBC News*, 5 January 2006).

Researchers have been attempting to develop a rotavirus vaccine since the 1970s. In 1998, RotaShield (Wyeth) was released on the market, but it was withdrawn within a year because a small number of individuals developed an intestinal blockage known as intussusception. Both of the new vaccines were therefore tested on a large number of infants (in Europe, the United States and Latin America). Neither vaccine seemed to cause intussusception. "These are milestone results", says John Wecker, of PATH (*New Scientist*, 14 January 2006), a US non-profit organization that is working with Merck & Co. and GlaxoSmithKline to set up trials in Asia and Africa.

Such trials are crucial, as Roger Glass and Umesh Parashar (Centers for Disease Control and Prevention, USA) write in *The New England Journal of Medicine* (5 January 2006): "Both vaccines will need to demonstrate their efficacy in the difficult settings of developing countries".

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Photograph by Daniel Jones

INFLAMMATION

T-bet links innate and adaptive immune responses

The transcription factor T-bet is best known for its role in T helper 1 (T_H1)-cell differentiation, but now new data indicate that T-bet expression by dendritic cells (DCs) is also required for pro-inflammatory cytokine production and T-cell priming.

Because T-bet is highly expressed in tissues affected by rheumatoid arthritis in humans, Glimcher and colleagues set out to evaluate the role of T-bet in a mouse model of arthritis, collagen-antibody-induced arthritis (CAIA). In this model, disease is induced by administration

INFLAMMATION

Switching on the inflammasome

Assembly and activation of the inflammasome is an essential process in innate immune defence. The inflammasome is a cytosolic, multiprotein platform that allows activation of precursors of pro-inflammatory caspases, which then cleave the precursor of interleukin-1β (pro-IL-1β) into the active form, the secretion of which leads to a potent inflammatory response. But little is known about the natural stimuli that lead to activation of the inflammasome and the mechanisms by which these stimuli accomplish this. Now, three studies published in *Nature* have identified bacterial components and endogenous 'danger' signals that activate inflammasomes that contain NALP3 (also known as cryopyrin).

> "these results show that NALP3 has a crucial role in host defence against certain bacteria and that it might be a proximal sensor of cellular stress and danger signals"

The central component of an inflammasome is a member of the NALP family, and this protein associates with the adaptor protein apoptosis-associated speck-like protein (ASC), which in turn recruits pro-inflammatory-caspase precursors (such as pro-caspase-1). NALP1, NALP2 and NALP3 have been shown to form inflammasomes, and the importance of NALP3 is well established, because mutations in the gene that encodes NALP3 (*CIAS1*) cause several autoinflammatory disorders. So, three groups of researchers set out to define the role of NALP3 in inflammatory responses. Each group independently generated NALP3-deficient mice and then examined macrophages from these mice for their ability to process pro-caspase-1 or pro-IL-1β and to secrete IL-1β in response to various microbial and non-microbial stimuli.

Núñez and colleagues examined macrophage responses to several Toll-like receptor (TLR) ligands and showed that NALP3 is specifically required for pro-caspase-1 cleavage and IL-1β production in response to the synthetic TLR7 ligands R837 (also known as imiquimod) and R848 (also known as resiquimod). These molecules are structurally similar to purine bases, so the authors also examined macrophage responses to bacterial RNA, which they speculated might be a natural ligand for NALP3, and they obtained similar results. Tschopp and colleagues similarly showed that crystals of monosodium urate (which

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