



nature publishing group



► **COVER:** 'Sifting through the cellular dustbin' by Susanne Harris, inspired by the review on p596.



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Our understanding of the complex signalling processes involved in inflammation has advanced considerably in recent years with the identification of new ligands, receptors and downstream pathway components. This month, O'Neill provides a comprehensive account of current knowledge about these signalling pathways and discusses the prospects for drugs targeting different pathway components. Intracellular signalling is rapidly and precisely regulated by targeted protein degradation via the ubiquitin–proteasome system (UPS). Harper and colleagues examine evidence that dysregulation of the UPS is involved in conditions ranging from neurodegeneration to cancer, and consider how to target this system therapeutically. Understanding how cells become immortalized in tumours will be important for anticancer drug discovery. Shay and Wright review the involvement of telomerase, which acts to maintain telomeres and bypass cellular senescence, in this process and evaluate strategies to target telomerase. An existing cancer therapeutic, rituximab, was instrumental in drawing attention to the role of B cells in autoimmune disorders, after reports of its efficacy in rheumatoid arthritis. Browning investigates the growing evidence for the role of B cells in diseases such as rheumatoid arthritis and systemic lupus erythematosus, and discusses approaches to modulate B-cell function, in particular with protein therapeutics. Effective delivery methods could enhance the utilization of such therapies, and in a Perspective article Mitragotri discusses the clinical applications of needle-free liquid jet injectors, emphasizing mechanical considerations that are important for the future development of these devices. And in our final review, Hofstadler and Sannes-Lowery consider how mass spectrometry, which is currently used extensively in characterizing potential drugs, could also contribute to compound screening and optimization.

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