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► **COVER:** 'Drugs and the immune system join forces' by Simon Bradbrook, inspired by the Review on p59.



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**L**ike many things in life, maintaining a fine balance in the immune system is the recipe for healthy living. In their Review on page 34, Falk Nimmerjahn and Jeffrey Ravetch focus on the family of Fc receptors for IgG (FcγRs) and describe how the generation of a well-balanced immune response requires the simultaneous triggering of both activating and inhibitory FcγR signalling pathways that set a threshold for cell activation. As they explain, perturbation of this balance can result in either responses that are insufficient to deal with pathogenic microorganisms or the loss of tolerance and the induction of autoimmunity.

On page 74, Andrew Mellor and David Munn also consider the question of balance between effective elimination of pathogens and inappropriate immune responses to self, although here the setting is on a local level. They put forward the concept of acquired local immune privilege and argue that, in any local setting, a shift in favour of suppressive over stimulatory mechanisms is an indirect consequence of the need to control the potentially lethal consequence of unrestrained immunity to innocuous substances.

Events occurring in one specific site — the germinal centre — have a clear beneficial role in immunity but this seems to be counterbalanced by their detrimental role in lymphomagenesis. As described on page 22, germinal-centre B cells have a unique physiology and specialized mechanisms that allow them to tolerate rapid proliferation and genetic remodelling without inducing a DNA-damage response. However, such events hold an obvious risk for cellular transformation and the development of malignancy.

Finally, the concept of balance is also paramount in the Opinion article by Michel Goldman and colleagues on page 81. They propose that microorganisms can tip the balance between the interleukin-12 family members and thereby control the outcome of T-cell-mediated inflammation.

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