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► **COVER:** 'Molecular epidemiology of pain' by Susanne Harris, inspired by the Perspective on p647.



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More effective treatments for neurological disorders including Alzheimer's disease and chronic pain are urgently needed, but although there have been major advances in the understanding of the underlying mechanisms, developing new drugs for these disorders has proved challenging. Our two perspectives this month consider these topics and provide insight into factors, such as interspecies differences, that have contributed to failures in the translation of research from the laboratory to the clinic. Dragunow discusses how the incorporation of an adult human brain preclinical platform might help overcome such hurdles in neurodegenerative drug development. Meanwhile Max and Stewart present the rationale for the application of human genome-wide association studies of pain phenotypes to accelerate the design of novel pain medications. Pain is among the diverse array of biological functions in which the nociceptin/orphanin FQ peptide and its receptor have been implicated. The physiology and potential clinical applications of modulating this system, as well as those agents that are currently available, are reviewed by Lambert. TGR5 was recently identified as a cell-surface bile-acid receptor. This discovery, together with the recognition that bile acids are also capable of modulating several nuclear hormone receptors, including the farnesoid X receptor, has led to the identification of novel roles for bile acids in metabolism. Thomas and colleagues review the diverse bile-acid-activated signalling pathways, highlighting strategies and agents that are currently under development for the treatment of metabolic diseases, including type 2 diabetes and obesity. Finally, in their Review, Tanrikulu and Schneider overview the concepts and methodologies behind pseudoreceptor modelling, discussing the potential and limitations of this strategy in drug design and highlighting recent applications in hit and lead finding.

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