Advancing our understanding of pain mechanisms and the need for improved analgesic treatments faces challenges in both clinical and laboratory domains. The preclinical approaches provide advances in our fundamental understanding of the neurobiology of pain, but the gaps between molecules and pathways to the patients need to be addressed.

Viewpoints differ on the notion that animal models are the culprits of the failure to produce new pain drugs. But perhaps, it is not a fault of the models, but the interpretation of the information provided by them? Pain measured in humans often relies on an analogue scale (i.e. a standard rating scale of 0–10). By definition, the threshold would lie around 2 and this is what is measured by reflex responses in animals. Consequently, a drug that is effective on threshold measures is likely to fail when confronted by the pain levels of 6–7 that patients in trials report. Here, a different approach to preclinical investigation of drug efficacy is needed. We confess to being besotted by neuronal responses obtained by in vivo electrophysiology, but these do provide an unbiased, objective measure of low and suprathreshold multi-modal responses in pain models. Indeed, these electrophysiological measures of neuronal activity likely equate better to clinical pains. But then again, we might be geeks...
from animals to patients.3–6 The new molecule tapentadol is a clever example signifying the value of preclinical studies that explore mechanisms of potential pain drugs. This opioid agonist with synergistic actions for blocking noradrenergic re-uptake was translated from animal models of neuropathy and inflammation to prove effective in both major types of pain, leading to further positive studies in lower back pain.7 We find it difficult to argue against the importance of preclinical investigations of drug targets, and after all, the mode of action of gabapentinoids, antidepressants in pain, ketamine analgesia, and ziconotide all came from preclinical studies and relate to important pain therapies in patients.8–11 Of course, animals cannot be expected to reveal the entire array of complex human side-effects, so our claims are based on efficacy rather than tolerability. The latter will only be revealed when the molecules enter humans, and here patients may have co-existing problems that impact upon side-effects.

We owe a great deal of our understanding of pain mechanisms to animal studies. Central sensitization (CS) comprises a series of key physiological events that contribute to the chronification of pain states. Studies conducted in animals have described the associated mechanisms of wind-up whereby a repeated noxious stimulus permits spinal NMDA receptor activation to drive enhanced neuronal responsiveness and enlarge their receptive fields. This is the most plausible mechanism behind mechanical allodynia, and indeed, CS and abnormal wind-up have been reported in many patient groups, so the concept has translated well.12 Genetic engineering has pioneered the identification of numerous ion channels ranging from sodium channels to transient receptor potential (TRP) channels. Their roles were revealed primarily by knock-out studies in mice, but there are now several known human channelopathies, including loss and gain of function of Na1.7 in humans, gain-of-function of TRPA1, and polymorphisms in TRPV1, all that allow forward- and back-translation of transgenic animal models.13–15 Other targets such as the P2X7 receptor join the list with further implications for understanding individual variations in pain.16

And it is more than just the molecules that translate. Our knowledge about the midbrain and brainstem circuitry that underlie descending controls and mediate spinal–supraspinal cross talk stems from animal studies.17,18 Spinal neurones that are activated by noxious input project to thalamocortical sites and generate the sensory discriminative aspects of pain relating to location and intensity, while other spinal neurones project in parallel to limbic areas. These latter ancient midbrain areas are involved in fear, anxiety, mood, and stress responses and thereby underlie affective and emotional aspects of a noxious stimulus. Anxiety, sleep disorders, and depression are all common co-morbidities in chronic pain patients that have a major impact on the suffering experienced.19 We have recently shown that neurones in the amygdala, a key centre for emotional memories and implicated in the central drive of descending controls, are altered after nerve injury.20 Asymmetric and time-related changes ensue, spanning the post-operative to the persistent neuropathic state. The association of pain with sleep disturbances, depression, and anxiety are explicable in terms of these networks.

Feedback from the higher centres of the brain project back to the spinal cord where further modulation of nociceptive information occurs. Balance between inhibition and excitation in descending pathways holds the key to the level of pain processing.17 In humans, imaging reveals similar anatomical systems recruited in placebo analgesia where inhibitions are produced, and in chronic pain states with abnormal facilitations.21–22 Diffuse noxious inhibitory controls are reduced in many human pain states and have been shown to be a risk factor in the transition from acute to chronic pain.23 Study of descending facilitatory and inhibitory pathways has not only improved our understanding of the mechanisms of drugs used to treat pain, such as the antidepressants, but also our knowledge of events underlying the persistence of pain states.

More recent studies have explored the eminent question as to why some people develop chronic pain and others do not. Fear and anxiety, and also pain intensity, impact on the provision of rescue medication after hysterectomy in the acute setting.24 Anxiety and the level of pain in the perioperative period have also been highlighted as risk factors for chronic pain after certain surgical procedures.25 Given the close association of pain and affect, it is likely that central sensitization can drive spinal, supraspinal plastic changes, or both that maintain high pain levels and impact fear and anxiety. These in turn shift the balance of descending controls towards facilitation. This balance between excitation and inhibition through descending pathways is critical in the development and maintenance of chronic pain—indeed, ablation of brainstem neurones at the origins of descending facilitations leads to a short-lasting mechanical hypersensitivity after nerve injury in animals that fails to become persistent.26 The role of the brainstem in maintaining pain states is further explored by a study by De Felice and colleagues27 investigating the incidence of the neuropathic pain phenotype, where in contrast to the majority of rat studies, only the minority of patients with neuropathy develop pain. Indeed, this has been put forward as a major criticism of the animal studies, but the argument in defence has always been that the strain of animal chosen exhibits the required behavioural endpoint after nerve injury. De Felice and colleagues have studied this in detail and shown that different strains of rats have different probabilities of developing pain behaviour after neuropathy. Clearly, the genetic background explains the difference and indeed the heterogeneity at the genetic level in humans likely underlies the reason why not all patients with neuropathy have pain. Particular genetic profiles are likely to protect or enhance pain, nerve damage and immune responses.13,16 Remarkably, De Felice and colleagues also demonstrated a recruitment of descending inhibition (partly noradrenergic) in the group of rats where 50% of animals had nerve damage with no pain. Crucially, this is in parallel with enhanced descending facilitations evoked by neuropathy. Although the degree and extent of peripheral damage was identical in all animals, in some cases chronic pain was shown to arise from continued peripheral input but in others, brainstem modulation could suppress the pain phenotype.

Clearly in cases such as the De Felice study, CS must engage brain circuits. However, from a defined spinal mechanism the
term ‘central sensitization’ is nowadays frequently used to cover any complex and often diffuse pain states. Wind-up and other manifestations of CS are seen in spinal circuits—the events do not need the brain. It is also hard to envisage a spread of excitability beyond a few segments through spinal mechanisms and most animal models of pain with peripheral pathology reveal changes confined to the damaged nerve territories or tissue. Clearly, CS can drive neuroadaptive changes in the brain. Many limbic brain areas have whole body receptive fields and the descending controls appear to be bilateral and diffuse in character. Thus, we should differentiate between spinal, localized CS and diffuse pains, likely consequent to altered excitability and neuronal activity of supraspinal centres.28

Another criticism of animal models is that measured endpoints usually relate to evoked pain whereas patients have major problems with spontaneous pain. However, ongoing activities in the absence of stimuli have been long recorded in neurones in animal preparations and of course; there are now several behavioural approaches to measuring ongoing pain. Yet, the clinical data on ongoing and evoked activity is still sparse. The use of conditioned place preference (CPP) is convincing but the effective agents against ongoing pain generally overlap with those effective on evoked pains.29 30 Clinical research has barely touched on this issue, so future human studies comparing drugs on evoked and ongoing pain are a key to effective back-translation. Here, study design is crucial to extract the most information from patients; the large majority of clinical trials on drugs simply asks the patient to report their level of pain, but how does the patient go about reporting this if one of these components (evoked or ongoing) was changed by a drug and not the other? One interesting mismatch has surfaced in this regard. TRPA1 is an irritant sensor and in pharmacological studies comparing CPP and evoked pain in animals with diabetic or surgical neuropathy, TRPA1 was reported to be involved in evoked mechanical responsibility but not ongoing pain.31 This may appear to be a bit too molecular if you are searching for the patient link, but bear in mind the inherited TRPA1 gain-of-function mutation leaves affected individuals with normal acute pain and no ongoing pain, but a pain syndrome that is triggered by external and internal factors, namely cold, fatigue, and hunger.15

Yet, we are still not convinced that the issue of measuring ongoing pain is simple. In a thought provoking review, Bennett32 has raised the issue that pain that may seem to be ongoing may in fact be evoked or triggered by normal daily events, such as the touch of clothes, the local environment or events, such as the touch of clothes, the local environment or changes in temperature if mechanical and thermal allodynia is present in the subjects. Of course, a further complication is that pain may wax and wane and fluctuate over the course of the day. This begs the question—have we really fully understood and reported the clinical incidents of spontaneous and ongoing pain? Only then would we be able to effectively model these in animals through back-translation.

Given that genotyping large numbers of patients is unlikely the most practical approach, sensory profiles might come to the rescue. Indeed, a promising success in phenotyping large patient cohorts is being led by the German Research Network on Neuropathic Pain (DFNS). Sensory profiling in patients will identify the most relevant components of the pain phenotype that robustly reflects the underlying mechanism/combination of mechanisms operating in the patients. Pharmacological studies could follow to inform on responses based on sensory profiles; in this case, certain pain descriptors could lead to a targeted treatment if particular sensory profiles can predict responses to drugs. Of the many issues that arise, one is that five sub-groups can be separated out in patients with neuropathic pain, and these are independent of aetiology.33 If two of the five groups respond to a treatment, it is highly likely that a clinical trial would fail, despite the drug being effective in patient sub-groups. It is essential to improve analgesic treatments by directing pain research towards individualized medicine. One way to progress would be to validate questionnaires for repeated testing in order to link symptoms and signs to treatments over a time course. In this regard, ongoing and different modalities of evoked pains could be gauged in the patients along with drug effects, bringing the human studies into alignment with the animal models.

Effective translation of pain research is easy when we speak the same language. The key issues to overcome are effective clinical profiling of pain phenotypes, followed by the appropriate use and interpretation of animal research. Linking ties between clinical and preclinical data is crucial for a successful translation of pain research into improved analgesic treatments.

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None declared.

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Pain research: what have we learned and where are we going

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