OUTLOOK

Stimulating the development of mechanism-based, individualized pain therapies

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Abstract | Biomedical science has greatly improved our understanding of pain in recent decades, but few novel molecular entities that address fundamentally new pain mechanisms have entered the clinic, despite dramatically increased pharmaceutical investment. Indeed, virtually all new analgesics approved over the past 25 years are derivatives or reformulations of opioids or aspirin-like drugs, existing drugs given for a new indication or older drugs given by a different route of administration. Here, we discuss factors contributing to this lack of innovation in therapies for pain and advocate public–private partnerships (PPPs) to translate new knowledge into more efficacious and safer treatments.

Many serious diseases, such as cancer, heart disease, diabetes, AIDS and arthritis are often associated with unrelieved pain. Despite major advances in the understanding of the molecular mechanisms involved in pain and considerable investment in pharmaceutical research and development in this field, there are still few analgesic drug classes — all of which have safety issues. Consequently, pain-related conditions frequently lack effective therapy and a wide variety of drugs, such as antidepressants, anticonvulsants and steroids, are often used off-label for chronic pain in the absence of evidence of safety or efficacy for a pain indication.

The current situation with drugs available for pain provides a strong example of the challenges and problems facing novel drug development in general. Recognition of these challenges has prompted the US Food and Drug Administration (FDA) to examine the 'critical path' for drug development — the continuum from prototype drug design/discovery, through preclinical and clinical development, to FDA filing, approval and product launch preparation — and conclude that part of the problem is a scientific one: we are using the evaluation tools and infrastructure of the last century to develop this century's drug therapy. As a result, the FDA has created the Critical Path Initiative (BOX 1), which is intended to stimulate and facilitate research and strategic efforts to tackle the problems in drug discovery and development.

In this article, we will focus on the discovery and development of novel analgesics and we will discuss several strategic barriers, suggested through consensus of expert opinion, that are potentially responsible for the paucity of new analgesics introduced into clinical practice[1]. Most striking is the dichotomy between the development of molecules with highly selective antinociceptive mechanisms *in vitro* and the practice of pain medicine, in which combination therapy with additive drugs that act through diverse mechanisms is standard.

A potential barrier to developing new therapies for pain is the use of animal models that have been validated using prototype analgesics (such as morphine and non-steroidal anti-inflammatory drugs (NSAIDs)) as they may limit compound selection to candidates that have a similar pharmacological profile. A second broad limitation to developing new analgesics is that existing clinical models for pain may not readily extrapolate to chronic pain syndromes. For example, a single-dose study in the oral surgery model, often used for early phase clinical trials and which is clearly inflammatory in origin, may not provide insight into the medical utility of a centrally acting drug for neuropathic pain, as these mechanisms may be not be activated following acute inflammation. Even if a drug shows clinical efficacy in an appropriate pain model, comparison of treatment groups by measures of central tendency (mean, median) and variation of the group around this measure (standard deviation, range) may limit our understanding of the benefits and risks to managing the individual patient's pain[2].

> "Pain-related conditions frequently lack effective therapy."

Improved animal and clinical efficacy models as well as more meaningful criteria for evaluating chronic painful conditions are required to develop new pain therapeutics. There is also a need to develop better incentives for the development of diagnostics that might provide additional insight into genetic, functional and anatomical aspects of pain. A significant barrier to innovation in analgesic drug development is the lack of funding for such ambitious projects. An example of a successful research consortium based on mutual cooperation and funding among industry, academia, the FDA and the National Institutes of Health (NIH) is the Osteoarthritis Initiative. The alternative, multiple uncoordinated efforts by various sectors, may actually impede progress by developing divergent recommendations and research agendas. The remainder of this article will discuss the barriers to innovation and other challenges in the development of new pain therapeutics in more depth and propose strategies to reinvigorate analgesic drug development.

The moving pain target

The mechanistic complexity of tissue injury, inflammation, signal transduction and pain pathways (FIG. 1) reflect multiple molecular

Box 1 | **The critical path for medical product development**

Analysis of the number of major drug and biological product submissions to the US Food and Drug Administration (FDA) over the past decade reveal a marked decrease in the number of new molecular entities[39]. These long-term trends clearly indicate that despite increased investment and progress in basic biomedical science and pharmaceutical research, progress in the medical product development process has dwindled. The development process — the 'critical path' to patients — is becoming a serious bottleneck to the delivery of new products. The FDA recognizes the need to intensify the agency's involvement in modernizing medical product development and has proposed the 'Critical Path Initiative' to stimulate and facilitate efforts to address this problem.

The critical path for medical product development spans the continuum from prototype design or discovery, through preclinical and clinical development, to FDA filing, approval and product launch preparation. Three dimensions of the critical path process are evident: first, the assessment of safety — how to predict if a potential product will be harmful. Second, an evaluation of efficacy — how to determine if a potential product will have medical benefit. Third, industrialization — how to manufacture a product on a commercial scale with consistently high quality. The science base necessary to evaluate and predict safety and efficacy, and to enable manufacturing, is different from the science that generates the new idea for a drug, biologic or device. In general, the National Institutes of Health and academia do not perform research in this area, indicating the need to develop mechanisms and incentives to foster research directed at improving the scientific base for the critical path, for example, for analgesic drug development. Critical path research is complementary to basic and translational research, and results in the creation of new tools for the product development process.

and cellular pathways that operate in parallel in the peripheral and central nervous system (CNS) to produce different forms of pain. This redundancy in pain signalling makes it unlikely that there is a universal analgesic that can intrinsically reduce all forms of pain[3]. Even if these simple schematics adequately explain the neurophysiology of pain transduction and transmission, the molecular events occurring at each level are driven by gene expression that changes over time, forming the basis for plasticity in the nervous system. Gene expression probably differs among individuals, over time and in varying tissues and types of injury, making it unlikely that a single 'magic' molecular bullet can be developed.

Multiple novel analgesic targets. The multiple mediators of pain and inflammation are products of injury-induced gene expression that lead to plastic changes in the nervous system and immune responses. These multiple molecules and mechanisms hint at novel strategies for analgesic drug development. Genomics and proteomics are identifying hundreds of targets that could be validated singularly and in combinations to selectively modify pathways of pain and inflammation. However, pathophysiological similarities within diseases or across individuals may be sufficiently prevalent to provide an incentive for pharmaceutical development. Validation of targets for smaller populations and rare diseases may require recognition as indications to foster pharmaceutical research and development. Intractable pain conditions with significant morbidity for individual patients, and society in terms of economic burden for hospitalization and end-of-life care, may require unique incentives to foster drug development and facilitate regulatory procedures. It is likely that the traditional strategy of targeting a single mechanism has been 'mined out' for opioids and aspirin-like drugs. Highly selective targets, for example, neurokinin-1 (NK-1) antagonists, have not translated to clinical utility, probably due to the multiplicity of pain pathways, underlying inflammatory mediators and genetic polymorphisms. An initial step to reinvigorate analgesic drug development may be to acknowledge the plethora of receptors, cells and genetic changes involved in nociceptive signalling, which suggests that targeting multiple events could help to determine the combination of drugs that yield effective analgesia for specific diseases and diverse patients.

The failure of currently available analgesics to control hyperalgesia and allodynia provides an example of the need to consider novel targets for analgesic drugs following injury-induced gene expression. Glial cells were not considered when presently available drugs were developed[4], but these cells are now known to have a role in nociception and clinical pain syndromes. Emerging evidence demonstrates that astrocytes and microglia release pro-inflammatory cytokines in the spinal cord that are active participants in the initiation and maintenance of pain facilitation induced by inflammation and damage to peripheral tissues, peripheral nerves, spinal nerves and the spinal cord. Glial activation following injury results in increased production of pro-inflammatory substances, including tumour necrosis factor (TNF), interleukin-1 (IL-1) and -6 (IL-6), that act on neurons expressing receptors for them in pain pathways[5–7]. Peri-spinal injection of antagonists of pro-inflammatory cytokine function prevents and/or reverses allodynia and hyperalgesia in virtually every animal model tested[4]. As with the failure of NK-1 antagonists to translate into clinical use, the physiological relevance of glial activation as a therapeutic target awaits verification in humans.

Other approaches to block the effects of pro-inflammatory cytokines released from activated glia involve interfering with intracellular signalling cascades, in particular the p38 mitogen-activated protein (MAP) kinase pathway. Compounds that inhibit p38 MAP kinase inhibit allodynia and hyperalgesia in animal models of peripheral nerve injury, peripheral tissue inflammation, spinal nerve injury and spinal cord inflammation, as well as after peri-spinal substance P and *N*-methyl-D-aspartate (NMDA) administration[4–8]. The recent demonstration of the analgesic efficacy of an orally-administered p38 MAP kinase inhibitor (SCIO-469), in comparison with an NSAID[9] in humans, holds promise for extrapolation to chronic inflammatory conditions in which analgesic efficacy would be additive with drugs acting on traditional analgesic targets.

Target validation

Although the number of potential drug targets identified by the pharmaceutical industry is estimated to have increased 10-fold with *in silico* analysis of the human genome[10–12], validation of these targets requires a large number of carefully phenotyped patients and controls[10]. The clinical measurement of pain and analgesic efficacy is sensitive to placebo effects, individual variations in pain measurement, which can be influenced by past experiences, and is not based on a homogeneous biological process across experimental pain paradigms, acute clinical pain models (for example, oral surgery) or chronic diseases (such as rheumatoid arthritis). Even though candidate genes are part of the clinical response, factors such as gender, ethnicity and psychological temperament may predominate[13], making the detection of responders and non-responders on the basis of genotype alone problematic.

Can we detect medical utility for analgesic drugs with novel mechanisms in humans? The promise of pharmacogenetics to identify new targets for analgesic drug development and subsequent improvements in the prevention and management of pain may falter on the reality of current methods and strategies. Animal models for screening drugs for analgesic activity have largely been validated on their ability to detect drugs with known analgesic effects in humans, that is, opiates and aspirin-like drugs. It is not surprising then that new molecules selected on the basis of activity in these models have similar pharmacological profiles to existing analgesic drug classes. The magnitude of the distortion from normal physiology when inflaming a rat's paw with carrageenan, for example, may not be suitable for detecting subtle analgesic effects, particularly of drugs that do not target anti-inflammatory

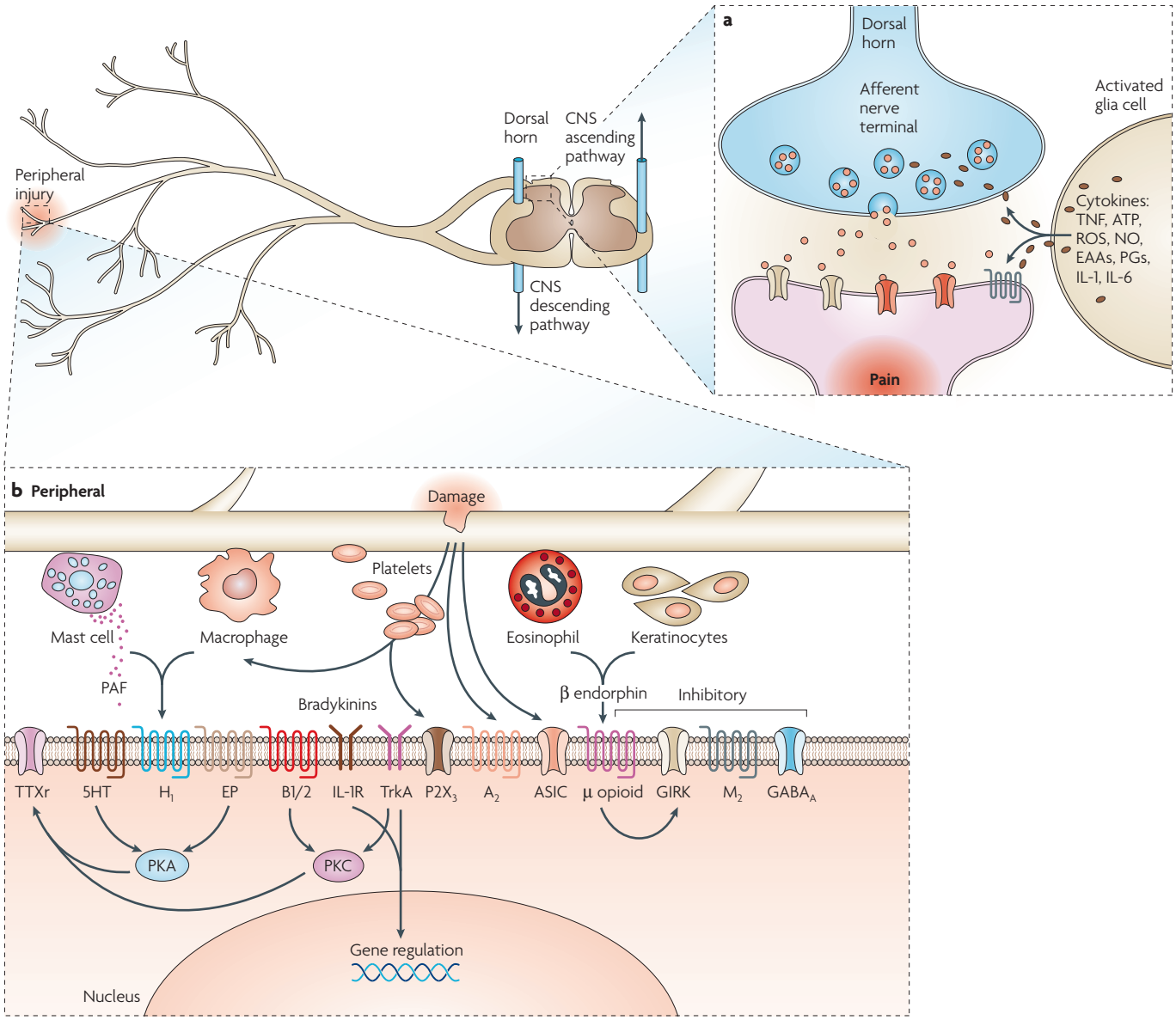

Figure 1 | **Schematic illustration of the 'moving pain target'.** Well-characterized receptors in the periphery are activated by noxious stimuli, tissue injury and acute inflammation, and send afferent information to the dorsal horn of the spinal cord where synaptic transmission to ascending pathways is subject to modulation by descending pathways, local neuronal circuits and a variety of neurochemicals. **a** | Neurochemical modulation of synaptic transmission in the dorsal horn showing examples of postsynaptic receptors and ion channels that are activated by excitatory amino acids released presynaptically and sensitized by cytokines from activated glial cells following nerve injury. **b** | Peripheral mediators of pain transduction after tissue injury: inflammation leads to the release of numerous chemicals from mast cells, macrophages and injured cells that act directly or indirectly to alter the sensitivity of receptors and ion channels on peripheral nerve terminals. These receptors release secondary messengers such as protein kinase A (PKA) and PKC that can activate other membrane bound receptors and gene transcription. A_2, adenosine A_2 receptor; ASIC, acid-sensing channels; B1/2, bradykinin receptors 1 and 2; CNS, central nervous system; EAAs, excitatory amino acids; EP, prostaglandin E receptor; GABA, γ-amino-butyric acid; GIRK, G-protein-coupled inwardly rectifying K^+; H_1, histamine H_1 receptor; 5-HT, 5-hydroxytryptamine; IL, interleukin; IL-1R, interleukin 1 receptor; M_2, muscarinic M_2 receptor; NO, nitric oxide; $P2X_3$, purinergic receptor X_3; PAF, platelet-activating factor; PGs, prostaglandins; ROS, reactive oxygen species; TNF, tumour necrosis factor; TTXr, tetrodotoxin receptor; TrkA, tyrosine receptor kinase A.

mechanisms. A striking feature of the path from drug discovery to demonstration of medical utility and commercial marketing is the inability to predict the ultimate success for a novel candidate. The development of animal models that are more predictive of changes in plasticity in the nervous system leading to hyperalgesia following the resolution of the initial injury could foster the development of drugs with anti-hyperalgesic properties, which is not necessarily the same as reducing spontaneous pain. The importance of this distinction is illustrated by an investigational antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors that did not have any effect on the traditional analgesic endpoint (spontaneous pain) but significantly reduced evoked pain in a clinical model, suggestive of an effect on the development of sensitization in the CNS[14].

Limitations of existing animal models and clinical trial settings also have the potential downside of recognizing drugs with mechanisms of action that are similar to those of approved drugs, while overlooking candidates with novel mechanistic targets. For example, the dental pain model has been used for years to successfully screen and compare the single-dose effects of compounds such as NSAIDs and cyclooxygenase-2 (COX-2) selective agents. However, analgesics may fail in this model for various reasons, such as bioavailability, or simply because the wrong pain model has been applied to the potential analgesic. If unique, and mechanistically non- (or minimally) overlapping pain models were available in which to conduct proof-of-concept studies, then unique and potentially synergistic analgesics might be identified and lead to therapeutic innovation.

Strategies for analgesic drug development

Analgesic drug development strategies have paralleled other areas of pharmacology and involve: identification and isolation of the active ingredient from naturally occurring compounds, for example, opium and willow-bark, modification of the structure to develop semi-synthetic and synthetic analogues, for example, heroin and aspirin, followed by structure–activity directed screening to identify drugs with greater specificity for the therapeutic effect without retaining the full range of adverse effects. The futility of this quest for specificity is exemplified by decades' worth of efforts to identify an optimal opiate drug[15], which has resulted in thousands of molecules that differ in potency, pharmacokinetic properties and routes of administration. It was belatedly recognized, however, that this series of opioid compounds retain the ability to produce similar analgesia and side effects, dependence liability and the development of tolerance when evaluated at equi-analgesic doses; these problems continue to plague opioid agonists to this day.

Recognition of the role of cyclooxygenase in pain and inflammation[16] led to the development of NSAIDs with greater analgesic and anti-inflammatory efficacy yet retaining the toxic potential of the aspirin-like drugs. Estimates of greater than 10,000 deaths annually[17] were attributed to NSAIDs before the recognition of these problems and the introduction of selective COX-2 inhibitors, which resulted in changes in clinical practice that appear to have increased gastrointestinal safety. Increasing selectivity for the COX-2 isoform appears to have further increased gastrointestinal safety[18,19] but at the expense of cardiovascular safety[20,21].

> "Combining several selective but additive actions in one molecule or a combination of molecules, systematically may allow the development of optimal ratios that have improved benefit."

Classic analgesic combinations arose from the necessity to provide greater analgesia without the dose-related adverse effects associated with increasing the dose of opioids and the ceiling of analgesic activity attributed to aspirin-like drugs. Although a combination of aspirin or acetaminophen (paracetamol) plus an orally-effective opioid, such as codeine or oxycodone, is generally recognized as an effective therapeutic strategy, fixed doses and adverse effects limit their clinical use for many applications. The multitude of analgesic mechanisms and pathways also limit the utility of drug combinations that are aimed primarily at opiate receptors and peripheral cyclooxygenase activity as other parallel pathways can still signal nociception.

Actions at multiple targets: lessons from antidepressants. The novel antidepressant duloxitine provides an example of a molecule with dual selective actions (it is a selective noradrenaline and selective serotonin reuptake inhibitor) that has improved efficacy and decreased adverse effects compared with agents that have a single selective action. The first generation of antidepressants, such as iproniazid and imipramine, affected many systems through multiple mechanisms of action, resulting in clinical efficacy but a wide range of adverse effects. The limitations of the adverse effect profile led to the development of analogues to minimize such undesirable effects (similar to early efforts to develop opioids that retained analgesic activity but minimized their adverse effects). A second wave of antidepressants focused on the development of selective reuptake inhibitors with increasing tolerability and safety compared with tricyclic antidepressants[22]. This strategy of developing antidepressant drugs with more specific mechanisms of action is at odds with the heterogeneous nature of major depressive disorders and appears to have reduced clinical activity[22-24].

The next phase in antidepressant drug therapy was the development of molecules that combine specific inhibition of serotonin and noradrenaline reuptake with the goal of offering greater benefit-to-risk ratio than selective reuptake inhibitors for just one of these mechanisms. Recognition that multiple peripheral and central receptors and pathways exist for pain, and that increasing selectivity leads to decreased analgesic activity provides a rationale for similar approaches in the development of analgesic drugs. Combining several selective but additive actions in one molecule, or a combination of molecules, systematically may allow the development of optimal ratios that have improved therapeutic benefit and adverse effect profiles that are appropriate for the disease and patient population. The design of clinical studies capable of detecting small increments in efficacy, for example, 20–25%, and additive effects of the same order of magnitude would be a prerequisite to demonstrate the analgesic activity of each ingredient and additive effects when used in combination. Effects of this magnitude might vary between individuals of varying genetic background and previous pain experiences so the development of scales capable of detecting effects that are meaningful for an individual patient, even if the overall mean effect for the group is modest, will be required.

Development of individual responder approaches. Individualization of drug therapy traditionally involves both drug selection and dose titration, customarily as a clinical decision for the individual patient[25]. This strategy is starting to be applied to

populations when making the decision to start a drug discovery programme or market a drug[25]. Factors contributing to individualization of drug therapy at the population level include pharmacokinetics and pharmacogenetics, an increased understanding of the molecular biology contributing to the disease processes and drug effects, and drug epidemiology. As research continues to subdivide diseases into smaller groups of more homogeneous patients, drug discovery is identifying compounds with activity for these narrowly defined diseases[25]. By contrast, analgesic drug development has been largely based on the mean responses of groups of patients with the same clinical condition given the same drug and dose, making identification of individual variation in efficacy or toxicity difficult to detect.

In a classic clinical pain trial design, the mean response of a group of subjects (N=30–50 per group) who were administered an investigational analgesic is compared with the mean response of other groups of subjects who were administered placebo or a standard analgesic drug. In pivotal analgesic trials, a failure to demonstrate a significant difference between treatment groups for efficacy or safety often forms the basis for considering the drug not worthy of further development. Little consideration is given to the efficacy or safety of the investigational treatment in individual subjects or subgroups of the patient sample tested, some of whom may have a very good response to the treatment or demonstrate greater toxicity, which taints the response of the group as a whole.

The FDA intends to issue a guidance document for enrichment designs that will emphasize genomic and proteomic biomarkers in 2009 (REF. 26). The responses of individual subjects in a clinical trial, which vary widely in genetic composition, past experiences, gender, ethnicity, expectations, disease processes and inflammation-induced gene expression, should be considered in the development and assessment of analgesic drugs (FIG. 2). It is unlikely that an analgesic drug would be uniformly effective under such heterogeneous conditions. Assessment of the individual patient's responses relative to generally accepted criteria for pain relief in comparison with the proportion of individuals that respond in appropriate control groups might reveal subgroups for which the treatment is particularly effective or results in unusual toxicity. Enriched enrollment trials that titrate patients at the beginning of a trial during an open-label segment to eliminate those who do not tolerate the drug while including those for whom it gives pain relief identifies responder subgroups. Enrichment designs in which biomarkers can reliably identify individuals that make up a potentially high response subgroup have greater statistical power to show a difference and could possibly result in an analgesic targeted at those patients most likely to respond[26,27]. A responder analysis approach might include: identification of drugs with therapeutic value for chronic pain that is resistant to normal therapies, development of drug classes with particular promise for pain in a particular condition (but not necessarily all types of pain) and identify molecular–genetic markers for predicting analgesic drug actions in individual patients.

Recent brain imaging studies provide evidence that subjective ratings of pain magnitude are closely related to objectively measured neural activity in a number of cortical regions recognized to be important in pain processing[28]. Inter-individual differences in these subjective reports of pain magnitude were closely related to the objectively measured degree of activation in these brain regions, providing evidence that differences in pain reported across patients reflect differences in the actual pain experience[29]. Although functional neuroimaging has provided an understanding of which brain areas are activated by acute painful stimulation, research on the neural pathways underlying pain modulation by cognitive, emotional, pharmaceutical and other factors has only just begun[30]. The influence of cognitive factors such as expectation clearly varies across subjects based on past experiences and is more likely

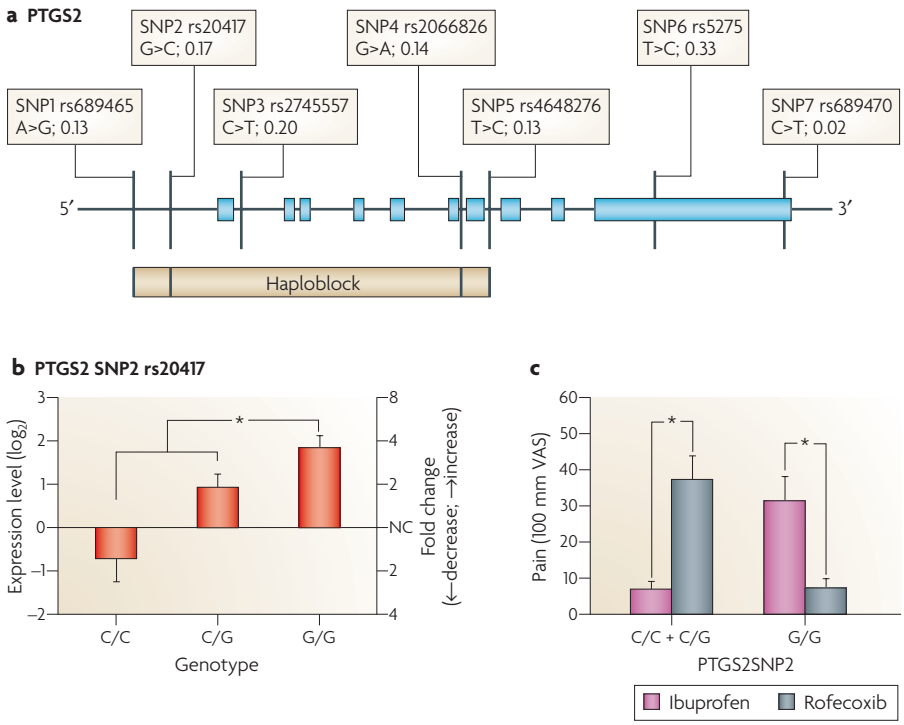

Figure 2 | **Wide variability in inflammation-induced gene expression across subjects alters the responseto analgesics.** Panel **a** illustrates the expression patterns of the gene for cyclooxygensase-2 (*PTGS2*) with its single nucleotide polymorphisms (SNPs); the first line in each box is the National Center for Biotechnology Information (NCBI) reference SNP ID number, the second line indicates the base pair exchange and the frequency of the minor allele. The blue boxes represent exons; vertical bars represent the location of SNPs and a haploblock spanning approximately 5 kb is shown as a yellow box. Panel **b** illustrates the expression level of *PTGS2* SNP rs20417 for the three genotypes; subjects with the minor allele homozygous C/C and heterozygous C/G showed significantly less ($P < 0.05$) *PTGS2* gene expression compared with those with the major allele homozygotes G/G. Panel **c** shows the analgesic response after surgery according to the SNPs in *PTGS2* after ibuprofen administration and rofecoxib. Subjects with a minor allele or who were heterozygous for *PTGS2* SNP rs20417 showed a significantly decreased pain response after ibuprofen administration ($P<0.05$), whereas the subjects who were major allele homozygotes (G/G) showed a significantly decreased pain response after rofecoxib administration. NC, no change; VAS, visual analogue scales. Figure modified with permission from REF. 43 © (2006) Macmillan Publishers Ltd.

to confound measurements across subjects. Assessment of individual responses may be less influenced by cognitive factors over the short duration of an analgesic study in which these factors are not likely to change.

Plasticity in the nervous system in response to pain is becoming generally accepted, but the identification of its manifestation in humans is still problematic. The development of quantitative sensory testing methods holds promise as a method to identify patients with central hyperalgesia and other manifestations of sensitization, but it is not possible at present to stratify subjects in clinical trials on the basis of potential central sensitization. The responses of subjects in a clinical trial, some of which may have altered pain processing due to central sensitization, might fail to discriminate patients who may benefit from a centrally acting analgesic, such as those acting on NMDA receptors. Careful consideration of individual responses might identify a subgroup that could benefit from a drug which is active against the aetiologic pain mechanism but not particularly useful for other types of pain, such as acute inflammatory pain, for example.

Age differences in postoperative pain and analgesic responses have been documented[31], but they may be scale dependent due to varying cognitive abilities or linguistic skills across age groups, or age-related changes in pain mechanisms. Use of mean responses across a group of subjects might not detect a meaningful change in pain intensity in response to an analgesic drug if subjects vary sufficiently in age to make the standard visual analogue scales (VAS) less sensitive to responses in elderly subjects than in younger subjects. The use of age-specific analgesic scales for children has been generally accepted and may serve as a model for developing pain scales for the elderly that take into consideration age-related changes in cognitive and psychomotor ability and visual acuity.

> “New clinical trials could then be powered based on calculations that take into account the proportion of patients that respond.”

Increasing evidence points to fundamental differences between males and females in their response to a nociceptive stimulus and variations in the neural circuitry that detects and modulates pain[32]. Women in general have lower thresholds to experimentally delivered somatic stimuli, greater ability to discriminate pain, higher pain ratings and less tolerance for noxious stimuli than men[33]. In general, males show greater activation of cognitive areas, central sympathetic areas and inhibition of limbic regions, whereas females show greater activation of affective and autonomic regions[34]. Studies in non-human mammalian models of pain also reveal sex differences in pain sensitivity[35,36]. Previous experience of severe pain during childbirth results in females rating their most intense pain approximately 20% greater than males, possibly changing subsequent pain reports on scales that use ‘most pain imaginable’ as an anchor[37]. These gender-related differences in pain perception, processing and subjective measurement may vary across females, as well as between males and females, to contribute to inter-individual differences in pain perception. One strategy for making valid comparisons across individuals could be the development of pain scales based on common sensory experiences[2,37]. In the case of taste, this was addressed by asking subjects to rate the (un)pleasantness of foods in the context of all previous pleasant and unpleasant experiences[37]; a similar situation could be envisioned for pain scales.

Inter-individual differences in analgesic responses to morphine are well-recognized; as illustrated by the range in self-administered doses needed to achieve adequate pain relief following general surgery[38]. Although the mean dose in this study was 13.2 mg of morphine, the range of doses in 3,045 patients was 1–48 mg, representing a 40-fold range of 0.02–0.83 mg per kg. Evaluation of an investigational analgesic with a similar potency to morphine at a fixed dose would probably produce inadequate analgesia in some patients, clinically useful analgesia in others and excessive adverse effects in others. The assessment of the overall efficacy and safety of an investigational drug using a mean effect in a sample[38] might fail to detect efficacy or predict an undesirable side effect profile, thereby masking the response of individual patients experiencing adequate analgesia with an acceptable side effect profile.

Trial design to discern individual analgesic responses. Sample size estimates for trials comparing means is calculated from standard formulae that require the definition of Type I and Type II error rates, standard deviation and the change to be observed in the means of the treatment groups of interest. For clinical outcomes that engender a single endpoint, such as a blood pressure measure, this approach has many advantages. However, for clinical outcomes that require consideration of more than one endpoint, a composite approach may be better able to encompass and accommodate these important variables. These composite endpoints can then be grouped into an index that is capable of defining, at the individual level, whether a particular patient did or did not achieve the endpoints in this composite index when the drug of interest was administered. A composite analgesic endpoint

Glossary

Cyclooxygenase-2
(COX-2). An enzyme that is expressed in cell membranes in response to tissue injury and catalyses the formation of pro-inflammatory cytokines from arachidonic acid.

Item response theory
Psychometric models that link patient responses to the probability of an underlying trait.

Haplotype
A combination of alleles or seqquence variations on the same chromosome.

Non-steroidal anti-inflammatory drugs
(NSAIDs). A structurally diverse class of drugs that block the enzymatic activity of cyclooxygenase to produce analgesia.

Off label
The use of an approved drug for a condition that is not mentioned in the original labelling.

Open-label segment
Identification of responders to a known drug by administration prior to randomization into the double-blind phase of a clinical trial.

Pharmacogenetics
The study of genetic variation that results in differing responses to drugs. Pharmacogenetics considers one or a few genes of interest, whereas pharmacogenomics considers the entire genome.

Plasticity
Changes in the nervous system that alter the processing of sensory information to augment or suppress the sensory responses elicited by a fixed input to a potentially painful stimulus.

Single nucleotide polymorphisms
(SNPs). Inter-individual differences in the DNA sequence at a single position in the genome, currently estimated to be greater than 10 million in the human genome. Differences in a single base could change the protein sequence, leading to differences in susceptibility to diseases or therapies.

Visual analogue scales
(VAS). A pain measurement scale consisting of a vertical or horizontal line, which defines a continuous response dimension between two words that anchor each end of the scale, usually ‘no pain’ at one end and ‘worst possible pain’ at the other.

Box 2 | **Strategies to reinvigorate analgesic drug discovery and development**

Problems confounding analgesic drug discovery

- Screening for novel molecules using animal models validated with opioids and non-steroidal anti-inflammatory drugs
- Validating analgesic activity with acute clinical models that may not be relevant to chronic pain
- Development of single entity analgesics with highly selective anti-nociceptive mechanisms
- Lack of funding for evaluating genetic, functional and anatomic aspects of pain in chronic painful conditions

Potential solutions

- Development of animal models that are predictive for blocking plastic changes in the nervous system leading to hyperalgesia
- Target multiple molecules and receptors involved in pain and inflammation
- Development of novel mechanistic clinical pain models to conduct proof-of-concept studies
- Development of research consortia to identify resources for critical path related pain research

would have to be validated in order to gain acceptance as a means of drug approval. New clinical trials could then be powered based on calculations that take into account the proportion of patients that responded to the outcomes measured by this index.

This approach has the advantage of grouping clinically important outcomes into a metric that defines the response of the individual, not the individual's contribution to a group outcome. Decisions could be made on the basis of looking directly at the response of the individual as part of the group rather than having to infer the person's response to the variable of interest as part of a large group mean or average response. In the latter situation, there is no way to understand whether two or more clinical outcomes of interest occurred in the same person, whereas in the responder approach this has been prospectively designed into the interpretation of data. For a clinical outcome in which the response of the individual is key to the proper interpretation of results, the responder approach offers the flexibility, both clinically and statistically, to best capture the patient's experience with the drug. Results similar to these can only be addressed with a means approach after substantial statistical efforts, such a multivariate analysis, with their problems of imputation artefacts and bias.

Pharmacogenetics is based on the principle that the individual responses of a patient to a drug regimen (the phenotype) can be related to some facet of their genetic composition (the genotype). If such links are observed in a sufficient number of individuals, it might be possible to derive a predictive relationship between genetics and individual therapeutic responses. Another promise of pharmacogenetics is the ability to identify potential adverse reactions that occur in a subset of individuals who react poorly to a treatment, sometimes related to metabolites of the parent drug. Given that most drugs are withdrawn from the market because of patient safety considerations, it may be more cost effective to identify individuals that are likely to experience toxicity due to a drug class, a particular drug or a drug dose. With an estimated 10 million single nucleotide polymorphisms (SNPs) in the human genome, the challenge to identify the relationship between SNPs and their haplotypes to individual variations in pain and analgesia may only be possible with responder approaches.

Reinvigorating analgesic development

A shift in the strategies used for analgesic drug development, from the mostly empirical to ones based on the multiple mechanisms of pain and pain pathways (BOX 2) could lead to the development of analgesics that act specifically and additively on the mechanisms involved. The multiplicity of symptoms, for example, hyperalgesia and allodynia, that comprise the pain experience are likely to result from specific and identifiable changes in the nervous system. Analgesia will not occur if the particular mechanism through which a drug interacts is not present in the patient. This extends to the clinical differences between acute and chronic pain, which may not represent distinct states of the nervous system. Acute pain refers to the pain experienced after the initiating event(s) and may be transient; chronic pain results from the persistence of the mechanisms activated by the tissue injury. The way to move forward clinically is to validate hypotheses about the mechanisms that convert a short lasting pain into persistent, intractable pain.

Pharmacogenomics represents another possible strategy for enhancing analgesic drug development and pain therapy if an individual's genetic profile influences their responses to analgesic efficacy or safety. The ability to identify subpopulations of patients that are responsive to drugs targeting specific molecular–genetic mechanisms has not been demonstrated, however, and even if valid, incentives may be needed to foster pharmaceutical investment in a 'non-blockbuster' market (which is still actually larger than that for an orphan drug indication).

Another approach to improve analgesic drug development is based on the fact that variability among clinical trials in outcome assessments has impeded evaluations of the efficacy and effectiveness of treatments for chronic pain[40]. This has lead an *ad hoc* group of pain investigators, federal regulators and representatives of the pharmaceutical industry, as well as the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT), to propose the development of a core set of outcome domains and measurement procedures to facilitate comparison and pooling of data. The IMMPACT consensus is that clinical trials should assess outcomes representing six core domains: pain, physical functioning, emotional functioning, participant rating of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition[40]. Consensus recommendations for specific measures of each domain have been proposed[41] based on the extensive pre-existing literature on patient-reported outcomes and taking into consideration the limitations of existing measures and the pressing need to develop improved methods for assessing chronic pain outcomes. Strategies for developing novel patient-reported outcome measures for pain clinical trials have been proposed[42] and the NIH has funded a collaborative project, Patient Reported Outcomes Measurement Information Systems (PROMIS), to examine the application of item response theory in areas related to pain and physical and emotional functioning.

Properly constructed individual pain response measures hold the potential to better capture outcomes in clinical trials, more so than approaching the same problem from a group or means perspective. Validating the role of an individual responder approach for clinical analgesic trials using potential biomarkers could reveal clinically important outcomes,

possibly leading to the identification of subgroups of patients whose underlying molecular–genetic pain mechanisms provide a favourable therapeutic ratio for an analgesic drug.

The Critical Path Initiative (BOX 1) has had a very positive response from the pharmaceutical and academic communities. The FDA has also published a Critical Path Opportunities list that identifies high return projects and will focus interest. The FDA has already identified many projects as part of the critical path process and work has begun as opportunities present. The development of research consortia to serve as both umbrella organizations and to address specific projects has already started (see Further information). Collaborations are underway in toxicology and oncology. In addition, further consortia are being created. Progress in critical path-related pain research will require the identification of parties willing to organize public–private partnerships (PPPs) and identify resources needed to start the process. The Foundation for the NIH was established by the US Congress to support the mission of the NIH and to advance collaboration with biomedical researchers from universities, industry and nonprofit organizations by forming PPPs with donors. The Foundation identifies partners (including organizations and individuals) and matches donors' interests to specific NIH needs. The Foundation fosters innovative programmes that can fill unmet needs which are not currently supported by standard funding sources. Similar approaches between Federal agencies, the pharmaceutical industry, philanthropic organizations and universities are being used to fund FDA or NIH-coordinated initiatives and should be considered for developing new pain therapies.

Treatment of pain remains a major unmet medical need and current research has not resulted in an optimal translation to the clinic. A PPP for pain may be the catalyst that is needed to enhance translation of scientific opportunities into improved pain relief for chronic diseases and their associated symptoms.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES
UniProtKB: http://ca.expasy.org/sprot
COX-2 | IL-1 | IL-6 | TNF

FURTHER INFORMATION
FDA Critical Path Initiative:
http://www.fda.gov/oc/initiatives/criticalpath/
Foundation for the NIH:
http://ppp.od.nih.gov/pppinfo/foundation.asp
Osteoarthritis Initiative:
http://www.niams.nih.gov/ne/oi/
Patient-reported outcomes measurement information system: http://www.nihpromis.org/
Predictive Safety Testing Consortium:
http://www.fda.gov/bbs/topics/news/2006/NEW01337.html

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