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CURRENT CHALLENGES IN TRANSLATIONAL PAIN RESEARCH

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Abstract

The current gap between basic science research and new analgesic development presents a serious challenge for the future of pain medicine. This challenge is particularly difficult in the search for better treatment for comorbid chronic pain conditions because i) animal “pain” models do not simulate multi-dimensional clinical pain conditions; ii) animal behavioral testing does not assess subjective pain experience; iii) preclinical data provide little assurance regarding the direction of new analgesic development; and iv) clinical trials routinely use over-sanitized study populations and fail to capture the multidisciplinary consequences of comorbid chronic pain. Therefore, a paradigm shift in translational pain research is necessary to transform the current strategy from focusing on molecular switches of nociception to studying pain as a system-based integral response that includes psychosocial comorbidities. Several key issues of translational pain research are discussed in this article.

Clinical pain

Despite the subjective and comorbid nature of clinical pain, pain is traditionally regarded as a sensory modality and a branch of sensory physiology. Over nearly five decades, basic science research has largely focused on understanding generation, transmission, and modulation of nociceptive signals. This effort has been substantially intensified over the past three decades owing to an explosion of neuroscience research with state-of-the-art techniques, generating a long list of tantalizing cellular and molecular targets for potential analgesic development [1, 2] (Table 1). However, few of these new targets have been successfully brought to clinical use [2] and many pharmaceutical companies have recently moved out of analgesic research and development. In the wake of this reality, some in the field question the validity of pain research using animal “pain” models, and others insist on continuing the current strategy that emphasizes the molecular and genetic mechanisms of nociception. As a physician-scientist in the field of pain medicine, I believe that a paradigm shift is needed in pain research that moves away from searching for molecular switches of nociception and toward studying pain as a system-based integral response that includes psychosocial comorbidities such as anxiety and depression. In this regard, translational pain research can play a unique role by developing innovative experimental paradigms and integrating multi-faceted research findings at the system level. In this article, I will discuss

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Conflict of Interest

I declare no conflict of interest.

several issues related to translational pain research and offer some thoughts on future directions.

Nociception versus clinical pain: a physician's perspective

Nociception is the neural processes encoding noxious stimuli that could create tissue damage, whereas clinical pain is what patient complains of the perceived actual or potential nociception. Currently, acute pain due to surgery or trauma can typically be treated with time-honored conventional analgesics including opioids and non-steroidal anti-inflammatory drugs (NSAIDs) because these drugs blunt nociceptive input. Coincidentally, the majority of new analgesics developed over the past five decades fall into these two categories [1, 2]. Other recent additions to the armamentarium of pain medicine include anti-migraine triptans, COX-2 inhibitors, mixed opioid agonist and norepinephrine reuptake inhibitors, and drugs approved for other medical conditions such as depression and epilepsy but increasingly being used for pain management [1, 2].

However, conventional analgesics are often less effective in alleviating chronic pain [3], and numerous examples of mismatches can be found between nociception and clinical pain (Figure 1). For instance, clinical pain can result from seemingly trivial tissue damage (e.g., complex regional pain syndrome) and outlast the duration of original injury. Clinical pain is also highly individualized in its intensity and quality depending on affective, autonomic and motor responses. Clinical pain, particularly chronic pain, does not correlate linearly with nociception and can be influenced by psychosocial comorbidities such as depression, anxiety, and catastrophizing in up to 50% of pain patients [4, 5]. This critical distinction between nociception and clinical pain, as well as pain-related psychosocial comorbidities, has been largely unaddressed in basic science research. Instead, the focus has been placed on understanding nociception, increasingly widening the gap between pain research and new analgesic development.

Challenges in pain research: a researcher's perspective

Given the distinction between nociception and clinical pain, the current strategy focusing on the cellular and molecular mechanisms of nociception would be understandably deficient due to a number of limitations in both bench and clinical studies. These limitations may explain some of the fundamental reasons as to why pain research has seen only tepid success in new analgesic development.

Limitations in bench studies

Three crucial limitations in bench studies are animal “pain” models, behavioral testing, and experimental paradigms. These are explored in detail below.

Most animal models of pain simulate a pathological condition such as complete Freund's adjuvant-induced hindpaw inflammation or sciatic nerve injury, whereas others mimic a disease entity such as bone cancer [1, 6–9]. Although rodents have anatomy and physiology that resembles those of human beings and can be used to study nociception, the goal of pain research is to understand *pain* and nociception is only part of this process. In this regard, animal models do not reproduce multiple dimensions of clinical pain including cognitive and affective changes. This deficiency may explain why we have had reasonable success in understanding physiological pain and acute pain in which nociception is the major driving force. By comparison, treatment of chronic pain continues to be a challenge because clinical comorbidities such as depression and anxiety, rather than nociception itself, are likely to be much more influential. Unfortunately, most currently available animal models do not account for such conditions.

Significant mismatches are present between nociceptive behavioral testing in rodents and pain assessment in human beings [1, 6, 10, 11]. First, the most commonly used behavioral tests in animal studies involve an evoked withdrawal response to thermal or mechanical stimulation, whereas clinical pain is self-reported by patients often as spontaneous pain in the absence of overt stimulation. Second, the modality of sensory testing in animal studies does not reflect common clinical situations. For instance, thermal hyperalgesia is the most frequently used behavioral testing in animal studies but it is hardly a characteristic feature of clinical pain. Third, the duration of animal studies is often brief (days and weeks), which does not adequately reproduce the impact of prolonged nociception on clinical pain.

Current experimental paradigms lay a heavy emphasis on the cellular and molecular mechanisms of nociception including synaptic plasticity without paying much attention to the role of system integration in pain and related comorbidities [1, 12–16]. This issue is further compounded by a disproportionate focus on primary order neurons and spinal cord mechanisms, and a bias towards exploring often redundant signal transduction pathways under a broad concept of neuroplasticity. Many sensational breakthroughs in the pain research field really are repetitions of known signal transduction pathways that have already been delineated in other specialties such as immunology, cell biology, and oncology but are reinvented in pain research using animal models of tissue injury. For example, many overlapping signal transduction pathways (e.g., protein kinase C, mitogen-activated protein kinases and their related intracellular pathways) are known to be involved in many biological functions and non-specific to nociception [1, 12, 16], although they have been shown to be sufficient and necessary in demonstrating animal nociceptive behaviors. This situation has left the field seriously puzzled as to which of these signal transduction pathways really is sufficient and necessary to serve as a target for new analgesic development.

Limitations in clinical studies

To date, few drug development targets identified in animal studies have been successfully brought to clinical use, such as neurokinin-1 (NK-1) receptor antagonists, TRPV1 antagonists, or NMDA receptor antagonists [2]. Some of these targets lack clinical efficacy (e.g., NK-1 receptor antagonists), whereas others cause significant side effects (e.g., hyperthermia by TRPV1 antagonists) [2]. Given the complexity of human pain experiences that can be influenced by genetic and psychosocial factors, three major issues are likely to have a significant impact on clinical pain studies: (i) mismatches between preclinical and clinical pain conditions and over-sanitation of human study subjects; ii) a dearth of meaningful clinical pain assessment tools; and iii) lack of understanding of pharmacokinetic, pharmacodynamics, and pharmacogenomic profiles and their interactions.

Several obstacles in clinical pain research increase the uncertainty of new analgesic development [1, 17–19]. First, mismatches are very common between animal “pain” models and actual clinical pain conditions, making it difficult to test those hypotheses coming out of preclinical studies. For example, although NMDA receptor antagonists are shown to be anti-hyperalgesic in animal studies of neuropathic pain, many human studies showed no effect of NMDA receptor antagonists (e.g., dextromethorphan, ketamine) because these studies used post-operative, non-neuropathic pain condition as a clinical pain model [1]. Second, over-sanitation of study subjects, in order to comply with scientific, ethical, and regulatory stipulations, makes many clinical studies far removed from the clinical reality. For example, strict inclusion and exclusion criteria are often used to enhance the power of clinical studies, such as age limit (e.g., 18–65 years old), a narrow range of pain scores (4 – 6 out of 10), and exclusion of comorbid conditions and concurrent use of other medications. This issue particularly affects studies of chronic pain because of its long duration and more complex clinical conditions. Third, many clinical studies are designed to test over-simplistic and

sometimes misinformed hypotheses (e.g., pre-emptive analgesia in patients with uncomplicated, acute post-operative pain) due to the lack of appreciation over the limitations in animal studies and technical difficulties in recruiting study subjects (e.g., for a 3-month longitudinal study that requires subjects to be off their usual medications and thus facing significant pain). In addition, clinical pain studies often focus on “spontaneous pain” rather than evoked pain symptoms such as allodynia (painful response to innocuous stimulation) and hyperalgesia (exacerbated painful response to noxious stimulation).

Visual analog or numerical pain scales used in human subjects are tools of a self-reporting system [20], which is clearly different from reflexive tests commonly used in animal studies. By the nature of self-reporting, this system does not have an anchoring value, varies among individuals, and could not be objectively verified [21]. Pain scales are typically influenced by clinical comorbidities such as mood swing, depression, stress, and anxiety; age, gender, genetic, and cultural differences; and placebo responders versus non-responders. Although clinical pain studies often include secondary measures to account for some of these factors [21], this complexity of clinical pain makes the margin of success exceedingly small in clinical trials of potential analgesics.

Differences in pharmacokinetic and pharmacodynamic profiles between rodents and human beings are frequent challenges in the design and interpretation of clinical studies [22–24]. These include the half-life of a drug, as well as its bioavailability, elimination, dosing regimen, receptor affinity, and side effect profile. Some compounds such as ziconotide (a peptide N-type calcium channel blocker) have very limited clinical utility because it can only be delivered intrathecally in its current formulation. In addition, animal studies typically test one compound at a time, whereas drug-drug interactions are an unavoidable reality in clinical practice. For example, in one study of more than 900,000 patients undergoing a urine drug test, 29% of the samples showed evidence of a non-prescribed drug in their systems, including 11% with evidence of illicit drug use [25]. Despite these confounding issues, few clinical studies are designed to simultaneously assess pharmacokinetic and pharmacodynamics profiles as well as their influence on the efficacy and side effects of pain medications [24].

A paradigm shift through translational pain research

Given the substantial gap between basic science research and new analgesic development, a major paradigm shift is needed in pain research. Although studying nociception is a fundamental aspect of pain research, we need to recognize that multiple dimensions of clinical pain cannot be addressed by understanding nociception only. In this regard, translational pain research must engage a new roadmap by integrating various areas of basic science and clinical studies. In particular, I suggest focusing on six key attributes of translational pain research.

Produce a new variety of animal models

It should be made unequivocally clear that animal models of tissue injury produce conditions of nociception, a gateway to pain research, but they are not a reliable surrogate of clinical pain. This deficiency in animal models may be mended by assimilating other features of clinical pain in these same models. In recent studies, tissue injury has been combined with behavioral phenotypes indicative of comorbid conditions such as depression, anxiety, or substance abuse in rodents. For example, in one model, rodents with genetically predisposed or induced depression and anxiety are exposed to tissue injury (e.g., sciatic nerve ligation) and both nociceptive and depressive/anxiety-like behaviors are then concurrently examined in the same rodents [26–28]. This new variety of animal models will be particularly useful to study chronic pain, as well as the transition from acute to chronic

pain, by adding a new dimension of clinical pain into an otherwise single dimensional (nociception) animal model. In addition, animal models need to account for gender and individual differences in clinical pain conditions [29–33]. Both male and female rodents may be included to compare the similarities and differences in their nociceptive response. Rather than relying on group analysis based on mean and standard deviation, rodents exposed to the same condition of tissue injury may be differentiated based on their onset, degree, duration, and recovery of nociceptive behaviors.

Transform the conceptual framework

A major setback in pain research is the lack of progress in new analgesic development [1, 2]. This situation is, at least in part, due to the current conceptual framework that appears to be biased towards studying redundant and parallel signal transduction pathways without a less concerted effort on the system-based data integration. For example, the transition from acute to chronic pain may reflect a shift from a mainly nociception-driven process to a progressively system-based response. Accordingly, a shift in the conceptual framework may be required by focusing on exploring the underlying mechanisms of disease entities that cause pain and uncommon mechanisms of pathological pain [34–36] and finding common pathways at the system (brain) level that regulate motor, autonomic, affective, and sensory dimensions of clinical pain [37]. We cannot conquer pain by simply dividing its mechanism into hundreds of single molecules. Pain is a system-based experience and must be studied and integrated at the system level.

Develop meaningful assessment tools

Several new tools have recently been introduced into basic science pain research, including measurement of operant performance (assessment of painful response based on performance of certain tasks), facial and behavioral profiling (correlation between facial features/ exploratory behaviors and the degree of nociception), and conditioned place preference or aversion (towards or away from an environment of nociception in response to a treatment) [38–43]. Although the validity of these tools needs further verification, they could potentially provide new measures complementary to conventional reflex-based behavioral tests. Another approach is that the reflex-based behavioral testing can be combined with behavioral phenotypes indicative of depression, anxiety, drug addiction, and cognitive changes to present a broader picture of “pain” behaviors in rodents [26–28]. For clinical pain, developing tools for “objective” pain assessment may be aided by biomarkers and neuroimaging techniques [44, 45]. Whether this approach is plausible remains to be seen and its success may largely depend on the progress in neuroscience and innovative technologies. In addition, clinical pain scales need to take into account the impact of pain medication itself on pain perception and pain mechanisms such as opioid-induced hyperalgesia [46] and medication-induced rebound headache [47].

Identify and distinguish biomarkers and genotypes of nociception and pain

Biomarkers are now considered such a crucial aspect of drug development that regulatory authorities in the EU and USA have come together to provide guidance on how to qualify and quantify novel biomarkers [48]. However, biomarkers of pain have been difficult to obtain. A fundamental misperception in the field of pain research is to consider biomarkers of nociception as the equivalent of biomarkers of pain. The former is a predictable outcome of tissue injury (e.g., release of cytokines) that produces nociception, similar to the clinical scenario of cardiac infarction that causes release of troponin. But identifying biomarkers of pain is a quite different proposition, perhaps an unrealistic one, as nociception does not predict the severity and duration of clinical pain. Recent studies have indicated a role for brain imaging in assessing clinical pain and predicting the pain chronicity [49–51]. An innovative approach would be to combine biomarkers of nociception with brain imaging

techniques such as PET and functional MRI to integrate both cellular and system responses. Genetic association studies including genome-wide association studies (GWAS) and epigenetic regulation have recently been integrated into pain research [52–59]. Although GWAS have identified dozens of candidate genes associated with experimental or clinical pain, many of these findings have been difficult to replicate, and results appear mainly clustered around 10 genes [59]. Thus far, genetic studies have failed to identify any one gene that explains a clinically significant amount of variance in susceptibility to or experience of chronic pain. Studying epigenetic regulation provides a useful tool to investigate the pattern of expression for a pool of genes related to a common clinical pain phenotype. However, a cautionary note to this line of research is whether this effort will simply embrace the same strategy of studying redundant and non-specific signal transduction pathways but at the genetic level.

Advance clinical pain research

An important task is to reform the current paradigm of clinical pain research that is often compromised by over-sanitation of study subjects and dependence on group statistics. Several new elements of clinical pain research include N-of-one study design, population-based data collection, post-marketing patient survey, and use of human models of experimentally evoked pain [60–62] (Table 2). The goal is to identify a true clinical profile comprised of individual responses and use such a profile to formulate individualized medicine. The success of new analgesic development may also require a significant reform of the current drug approval process stipulated by the US FDA, which often leads to the widespread off-label use of new analgesics once they are approved for a narrow therapeutic indication. For example, in addition to pain score, a broader spectrum of clinical outcomes including functionality and improvement in pain-related comorbid conditions may be used to constitute a composite score to examine the effectiveness of new analgesics for chronic pain management. In addition, new candidate drugs with indications for specific pain symptoms such as allodynia and hyperalgesia may be processed differently for approval as compared to conventional analgesics, because allodynia and hyperalgesia are evoked pain symptoms that are often episodic and fluctuate over time in the clinical setting.

Select new targets for drug development

A recent preclinical study suggests that the comorbidity between pain and depression may be concurrently treated by inhibiting brain indoleamine 2,3, dioxygenase, a rate-limiting enzyme in tryptophan metabolism [27]. This raises the possibility that clinical pain and related comorbidities may be effectively treated by targeting their underlying causes instead of symptomatic management using multi-drug therapy such as the combination of analgesics with antidepressants [3]. It also appears that new candidate drugs that could diminish nociceptive signals at the peripheral site, such as chemokine inhibitors and topical agents (Table 1), would be more attractive than those that target redundant intracellular pathways implicated in the central mechanisms of nociceptive processing.

Concluding remarks

Significant progress has been made in pain research over the past five decades. As a result, much has been known regarding the mechanisms of nociception (generation, transmission, and modulation) at the peripheral and spinal cord level. This has led to the significant improvement in clinical management of acute and post-operative pain. What remains challenging is chronic pain that is often disproportionate to the degree and duration of nociception and is heavily influenced by psychosocial factors. I believe that the most pressing issue in pain research is to develop and validate a new variety of animal models that are capable of integrating persistent nociception with pain-related comorbidities,

thereby facilitating a paradigm shift from focusing on molecular switches of nociception to studying chronic pain as a system-based integral response. In this regard, translational pain research will play a pivotal role in advancing pain research and pain medicine. The framework of translational pain research should not be limited to a process commonly referred as “from bench to bedside”. The success of translational pain research can improve new analgesic development and facilitate the transition from research to clinical application.

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Figure 1. Nociception versus clinical pain

Clinical pain is a multi-dimensional subjective experience consisting of sensory, motor, cognitive, autonomic, and affective responses and influenced by three key elements. (1) Nociception is a response to tissue injury that generates nociceptive signals. This process is likely to be less variable among individuals. (2) Pain perception in response to nociceptive input can be influenced by clinical comorbidities and personal experiences. (3) Pain response would determine the clinical course of pain and pain management.

Table 1

A partial list of potential targets for new drug development

Compound	Target	Phase of development	References
Qutenza® (Capsaicin 8% Patch)	Transient receptor potential vanilloid subfamily channel 1 (TRPV 1) agonist	Approved for use of post-shingles pain	63
ABT-102, DWP-05195, GRC-6211, MK-2295, SB-705498	TRPV1 antagonist	Phase I completed	64, 65
Cannabinor	CB2 agonist	Phase IIa completed	http://www.pharmoscorp.com/development/cannabinor.html
Ziconotide	N-type calcium channel blocker	Approved for clinical use for chronic pain	66
phenytoin, carbamazepine, and lamotrigine	Voltage-gated sodium channel blockers	Approved for epilepsy, used off-label for pain	67
A-317491	Purinergic P2 receptor antagonist	Preclinical	68
Tanezumab	humanized anti-nerve growth factor antibody	Phase II halted due to adverse events, but FDA recommends continued testing	69
Adenosine, GW493838	Adenosine receptor agonists	Adenosine itself is in clinical use; GW493838 has completed Phase II trials	70, Clinical trial ID: NCT00376454
SB681323, GW856553 ARRY-371797	p38 MAPK inhibitor	Phase II completed	Clinical trial ID: NCT00390845; NCT00969059; NCT00663767
Ketamine, Memantine	NDMA antagonist	Phase II recruiting	71, Clinical trial ID: NCT00961194; NCT01602185
(±)-HIP-A, (±)-HIP-B <i>cis</i> -ACBD	Glutamate transporter inhibitors	Preclinical	72
ABT-594	Nicotinic receptor antagonist	Phase II completed	73
5-hydroxydecanoate	Potassium channel blockers	Preclinical	74, 75
SSR150106, CCX354-C	Chemokine inhibitors	Phase II completed	76; Clinical trial ID: NCT00545454; Clinical trial ID: NCT01242917

Table 2

New tools of clinical pain research [60–62]

Study paradigm	Brief description	Utility in clinical study
N-of-one study design	Single case-based clinical trial	Analyze individual response
Population-based data collection	Collection of a wide spectrum of clinical data without pre-determined inclusion and exclusion criteria required for randomized clinical studies	Collect actual clinical data from a large cohort of patients; useful for data mining
Post-market patient survey	Collection of clinical data from patients receiving a new drug treatment	Assess the clinical effectiveness and side effects of a new drug in actual patients
Enriched enrollment	Enrollment of only those subjects who respond to, or exclusion of those who do not, a study drug or a drug with the similar effect to the study drug	Improve the study power; useful for prove-of-concept trials
Human experimental models of evoked pain	Evoked pain in human subjects using nociceptive stimuli such as capsaicin, heat, or mechanical pressure	Assess evoked pain as compared to spontaneous pain without overt stimulation