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2020 Foresight: Envisioning Therapeutic Innovations for Pain

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“Pain is a gift” is an adage frequently told to medical students to imply the important protective role of pain sensation against tissue injury. However, when pain persists and turns from a warning signal to a continually annoying or distressing symptom, it can hardly be called a gift. Chronic pain results in continual suffering in millions of patients and affects their work performance and quality of life with a large socioeconomic impact on the patient and the community [1].

The magnitude and consequences of pain cannot usually be ignored. Ever since the early civilizations when bark and leaves of the willow were used to treat painful conditions, clinicians have sought to put an end to people’s suffering. Yet a satisfactory cure for chronic pain, particularly that of neuropathic origin or consequent to bone metastasis, has not been achieved. As reviewed previously [2], there are several reasons contributing to this failure, including the limitation of the present animal and experimental clinical models of pain to identify novel analgesics other than those with mechanisms similar to the drug class that they were originally designed to test. Most of the present models were primarily designed to study molecules targeting a narrow scope of pain targets, which make them unsuitable to screen new investigational drugs targeting newly recognized or the still unidentified wide array of mediators and molecular-genetic modulators of pain. We review here emerging new approaches to analgesic development that promise to translate molecular-genetic findings of the past decade into new therapies by 2020.

Pharmacogenetics: A dream that will come true

The integration of pharmacogenetics to pain therapy in an effort to improve pain management by individualization of therapy might sound overly optimistic today. Yet with continuous improvements in genomic technology and single nucleotide polymorphism (SNP) screening and identification, it is not unexpected that screening for specific SNPs before deciding the treatment plan for pain would become as routine as measuring platelets count before prescribing heparin is routine nowadays. We have shown that variations in the gene expression of COX-2 as well as the analgesic efficacy of the non-steroidal anti-inflammatory drug ibuprofen and the selective COX-2 inhibitor rofecoxib are functionally associated with a SNP in PTGS2 [3]. Others have shown variability in morphine pain relief associated with genetic polymorphism [4,5]. Further, polymorphisms affecting drug-metabolizing enzymes and drug transporters that impact the pharmacokinetics of some drugs

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are increasingly being identified [6]. This continuous emergence of data makes the dream of individualizing pain management closer every day.

Analgesic Research is Evolving from the Hot Plate to Genomics

The development of new investigational techniques in the past few years allows for the identification of multiple new targets that may evolve to a completely new approach to pain management. Among these new techniques, microarray and proteomics are of particular interest. While microarray screens the human genome, whether DNA or RNA, proteomics is based on new technology that quantitatively investigates the composition of proteins and provide data about protein isoforms, posttranslational modifications interactions and stability [7]. Thus, they add new valuable information to the quest for analgesic targets, considering that protein and not DNA or RNA is the ultimate functional unit. Though proteomics is not yet a fully developed technique for high-scale analysis, it may represent a starting point in new drug development [7]. Recent studies using the technology of proteomics for the study of neuropathic pain suggest a number of new proteins that are involved in the process including metabolic enzymes that were regulated to meet the altered energy requirement of dorsal root ganglia cells following ligation [8]. Other proteins regulated following spinal root ligation include circulatory proteins participating in homeostasis and inflammatory response, extracellular matrix protein, proteins important for the functional and structural integrity of peripheral nerve, membrane-associated proteins in signal transduction, proteins associated with transcription and translation and proteins in defense against oxidation and neuronal cell death [8]. Table 1 lists some of these proteins. However, it is a long way from targeting any of these newly identified proteins to the development of a possible pain therapy.

Epigenetic Targets for Analgesia

The study of heritable changes in gene expression that are not due to changes in DNA sequence but rather to changes in DNA and DNA-binding proteins resulting in altered chromatin structure (epigenetics) is another field that may offer insights into pain management. Epigenetics can provide tools to better identify targets contributing to the pathogenesis of pain, as well as therapeutics based on epigenetic mechanisms. A prominent example is RNA interference (RNAi), which is a new technology of RNA-based therapeutics that promises to be useful in the management of different conditions by targeting molecules that are impossible to target with the existing medicines [9]. RNAi is achieved by a double stranded small interfering RNAs (siRNAs) that lead to the degradation of their cognate messenger RNAs and subsequently reduced content of the proteins they encode [10]. The past 20 years have shown several scientific and technical advances in the field of RNA-based therapeutics. However, other obstacles still obstruct the pathway towards using this new technology in the clinic, and resulting in only three molecules on the market and a handful in early phases of clinical trial [11].

RNAi have been investigated in experimental animal models of pain and show promising results. Different targets tested in-vivo include P2X3 [12], the NR2B subunit of N-methyl-D-aspartate (NMDA) receptor [13], transient receptor potential vanilloid receptor 1 (TRPV1) [14], and the tetrodotoxin-resistant sodium channel $Na_v1.8$ [15]. De novo DNA methylation, another important mechanism of epigenetic regulation of gene expression is implicated in the mechanism underlying the development of CFA-induced hyperalgesia in mice, and may provide a novel strategy for attenuating chronic pain [16].

Future Analgesics: Moving beyond Derivatives of Willow Bark and Opium

Consequences of tissue injury and inflammation have been studied for years resulting in a wealth of information about signal transduction and pain pathways, and still everyday brings new pieces of information that add to our understanding of the complexity of these pathways.

Multiple molecular and cellular pathways interact to produce different forms of pain, creating a wide array of new targets for future analgesics. This view of the complex multimodality pathogenesis of pain has led to the introduction of over 40 different new investigational molecules belonging to various classes of drugs. Among these are TRPV agonists, cannabinoids receptors agonists, glutamate antagonists and cytokine inhibitors [17].

The TRP family of ion channels is subdivided into 6 subfamilies according to amino acid sequence homology. Several TRPs have been described in dorsal root ganglia; TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8 [18,19]. The contribution of these channels to the generation of pain sensations is being revealed everyday, many of which are related to the first cloned subtype TRPV1 [20]. This is expected due to the longer availability of both a knockout mice strain and a specific antagonist (capcazepine) to TRPV1. It is suggested to play a role in inflammatory and neuropathic pain [21,22], visceral pain [23] as well as, cancer pain [24]. The generation of mice lacking functional TRPV3, TRPV4, TRPA1, and TRPM8 facilitates studying the role each of these subtypes play in pain. TRPV2 knockout mice were also recently generated [25].

The involvement of cannabinoid CB₁ and CB₂ receptors in pain modulation is well established [26,27] and the use of cannabis for the treatment of pain dates back to the 19th century when a British army physician serving in India noted its analgesic properties [28]. However, psychotropic adverse effects represent a major problem delaying the progress in the field of cannabinoid-based analgesics. Endogenous cannabinoids play a recognized role in pain as well and their preservation by inhibiting fatty acid amidohydrolase (FAAH), which has proven to have an antinociceptive effect in experimental animals. It is however, interesting that the antinociceptive effect of FAAH inhibition was not merely due to activation of CB₁ and CB₂ receptors, but other mechanisms are also involved [29]. The interaction between cannabinoids and TRPs in general and endocannabinoids and TRPV1 in particular has been discussed earlier [30,31], which complicates the picture. Recently, a new role for endocannabinoids has been revealed as mediators of activity-dependent sensitization in the neuronal circuits of the dorsal horn [32].

The key excitatory neurotransmitter, glutamate, plays a central role in pain transmission, through activation of ionotropic and metabotropic receptors (mGluR) [33]. Ionotropic receptors include NMDA, AMPA (α -amino-3-hydroxy-5-methy-4-isoxazole propionate) and kainate receptors. Because of the wide availability of studies identifying the role of NMDA receptors in pain processing, they have been a target for development of new analgesics for years. However, NMDA receptor antagonists have not lead to the expected pain relief [34]. The identification of NR2B subtype of NMDA receptor and its role in pain suggests a new target that may lead to effective results in both cancer pain [35] and neuropathic pain [36]. New strategies for targeting NMDA receptors include the transporter systems that regulate the concentration of glutamate at the synaptic cleft and the intracellular proteins involved in NMDA receptor signaling pathways [37]. AMPA/kainate receptors also contribute to spinal central sensitization in inflammatory pain [38,39]. At the molecular level, phosphorylation of AMPA and NMDA receptor subunits results in pain hypersensitivity. These molecular

pathways may also present a new target to counteract the undesirable effects of glutamate receptors activation.[40].

As for mGluRs, their role in the modulation of pain has been recently reviewed [41]. Negative allosteric modulators (NAM) of mGlu5 receptor show antihyperalgesic properties in animal studies [42], and recently in a phase II trial, ADX-10059, an NAM, was found to be effective for migraine prophylaxis [43]. Activation of mGlu2 and 3 on the other hand, may be analgesic [44], which present an interesting possibility to use molecules that cause endogenous activation of mGlu2/3 in pain management [41]. Recent studies on the role of group III mGluRs in pain modulation suggest an antihyperalgesic effect of their agonists [45]. However, further studies are needed to complete the picture and elucidate the possibility of these receptors as a target for chronic pain management.

The recognition of the multiple interactions occurring among pain mediators adds to the complexity of developing therapeutic strategies. The differential contribution of each of these mediators to different kinds of pain, further complicates the analgesic target, minimizing the likelihood of developing a single 'magic' molecular bullet to treat all kinds of pain. For example, Na_v1.8-expressing neurons were recently shown to be essential for mechanical, cold, and inflammatory pain but not for neuropathic pain or heat sensing [46]. Meanwhile, recent data suggests cross-talk between CCR2 (the CCL2 receptor, which also plays a role in pain) and TRP channels [47]. Similarly, TRPV1 plays a role in TNF- α -induced thermal hypersensitivity [48].

Complex interactions likely contribute to the development of central sensitization and plasticity. The role of plasticity in pain is becoming generally accepted. In experimental animals, neonatal chronic inflammation alters sensitivity to pain in adulthood, consistent with modulation of primary afferent activation and central sensitization in response to a subsequent nociceptive challenge in adulthood [49–51]. The translation to clinical practice is still not clear as conflicting results are reported, e.g. [52,53]. Loss of synaptic inhibition that occurs during the course of inflammation or neuropathy plays a significant role in plasticity [54,55]. Recently, GABA_A receptors containing the α 2 and α 3 subunits were identified as critical components of spinal pain control [56]. Therefore, a molecule that targets those subtypes sparing the α 1 benzodiazepine-site might represent an innovation for a non-sedative analgesic to test in chronic pain syndromes.

Rostroventromedial Medulla (RVM): an incomplete story

RVM is recognized as a relay in descending modulation of nociception, whether facilitatory or inhibitory [57]. Descending inhibition was recently suggested to involve an interaction between μ opioid receptors and TRPV1 to increase glutamate release into RVM leading to analgesia [58]. Descending facilitation from the RVM on the other hand, is responsible for the maintenance of chronic pain [59,60] and central sensitization in the dorsal horn of spinal cord that contributes to it [61]. Recent data shows that the majority of RVM cells expressing μ opioid receptors, co-express cholecystokinin type 2 receptors, suggesting that these cells may represent a new target for treatment of neuropathic pain [62].

Microglia: Evolving from Neuronal Glue to Complex Neuromodulators

Activated microglia are considered to play an important role in central sensitization following peripheral nerve injury [63]. Recognition of the role of glia in the central nervous system has been dramatically changed over the years from being considered as non-neuronal cells that provide support and nutrition for neurons to becoming central neuromodulatory, neurotrophic and neuroimmune elements [64]. For pain especially, glial activation is not simply correlated with exaggerated pain, but rather is increasingly implicated in the etiology

of pathological pain [65]. Glial activation in the RVM is suggested to participate in descending facilitation seen in inflammatory pain conditions [42]. Further, it is now recognized that many of the receptors expressed by neurons and astrocytes are also expressed by microglia [66] and activation of glia leads to the release of several pain mediators, including nitric oxide, prostaglandins, and excitatory amino acids, enhancing substance P and EAA release from primary afferent neurons [65].

In addition, glia has been shown to produce inflammatory cytokines including interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF) and interleukin-6 (IL-6) in response to peripheral inflammation that contribute to the development of chronic pain [67]. Not only inflammatory cytokines but chemokines as well, are now recognized to play an important role in the various types of acute and chronic pain both peripherally [68] and centrally [69]. Taken together, cytokines and chemokines represent new targets for pain therapy but awaits identification of the right combination of modulation to present a successful strategy for the management of chronic pain. A newly developed drug, tocilizumab (pending FDA approval) is an IL-6 monoclonal antibody that showed successful results in patients with rheumatoid arthritis [70], may be worth a trial in patients with chronic pain. Certainly, the future will bring several more of these bioactive medicines targeting different cytokines and chemokines. Though they represent a plausible approach for pain management, translational studies are needed to demonstrate translation to analgesia before clinical drug development can be ramped up.

Another role that has been attributed to glia is being a part of the neurovascular unit comprising the blood brain barrier (BBB). Interestingly, peripheral inflammatory pain results in BBB dysfunction [71]. Cytokines and other inflammatory mediators induced by peripheral inflammation results in the induction of CNS inflammation and gliosis with a resultant changes in the integrity of the BBB neurovascular unit altering the transport of drugs to the CNS [72].

Several glial modulators belonging to a diversity of pharmacological classes have been considered for the management of chronic pain including the tetracycline minocycline [73], the phosphodiesterase inhibitor ibudilast [74] and several others [64]. However, the use of glial modulators for chronic pain is still in early stages and contradictory results are reported [75].

Beyond New Drug Development

Besides the development of novel pharmacological entities, the current view of the complex pathophysiology of pain, the multiple targets contributing to the development and maintenance of pain and the interaction among these targets necessitates changes in the medical practice of pain therapy. For example,

- The use of multimodal pain management with a combination of preventive analgesic techniques involving both central- and peripheral-acting analgesics and novel devices [76].
- Development of multi-pronged interventional pain management programs including education, treatment, research and certification [77] and exploring augmentation of psychosocial and spiritual healing even when there is no chance of cure [78].
- Greater understanding of the symptoms biology of pain related co-morbidities such as fatigue and depression that limit the overall response to pain management.

- Exploring the possibilities of complementary and alternative medicine (CAM), which is becoming more accepted by the public. With this expanding use of CAM practices, it is very important to work on the validation of these practices using scientific methods. The National Center for Complementary and Alternative Medicine (NCCAM) was established in 1999 as an independent center at the NIH and works to explore CAM practices in the context of rigorous science. CAM approaches to manage pain include acupuncture, chiropractic and the use of magnets. Recent studies evaluating the effect of acupuncture for treating knee osteoarthritis and low back pain showed clinically relevant improvement in pain compared with patients in usual-care control groups but not compared to sham control, raising a question of whether these benefits may be due to placebo effect [79,80].
- Development of new techniques for assessment of pain that does not depend entirely on the subjective report by the patient might be an important step towards the development of new analgesics. Functional magnetic resonance imaging (fMRI) may represent a potentially useful technique to detect, in a non invasive manner, different biomarkers of pain [81,82]. Though there are some methodological considerations that still needed to be taken care of, its use has been shown to be a sensitive tool in assessing a potential drug effect. However, it is not unexpected that such functional imaging techniques will be useful in the near future as a tool with high sensitivity and specificity for evaluating analgesic agents [83]. Positron emission tomography (PET), and magnetoencephalography (MEG) are two other techniques for functional brain imaging. All the three techniques are employed to study cortical processing of pain. [84]. These technologies were of particular help in the study of cortical reorganization associated with chronic pain. Cortical reorganization and maladaptive neuroplasticity are thought to participate in the pathology of chronic neuropathic pain [85]. Recent study on patients with herpes simplex virus infections showed that cortical reorganization may occur even in the absence of peripheral nerve damage [86]. Studying cortical reorganization and its relation to chronic pain may provide new therapeutic approaches to management of this problem.

The expanding picture of different mechanisms involved in pain processing and the introduction of new technologies everyday to support pain research is without doubt a step forward towards the progress of pain management, a yet major unmet medical need. It is therefore expected that these developments will contribute to shape pain management in the coming years in a hopefully more individualized, efficacious and safe strategies.

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Table 1

Example of proteins modulated in different pain models as detected by proteomics

Protein	Regulation	Pain Model	Ref.
ATP synthase alpha subunit precursor (EC3.6.1.3)	↓	chronic compression of dorsal root ganglion for 28 days	[87]
Tubulin beta-5 chain	↓		
Ubiquitin carboxyl-terminal hydrolase isozyme L1	↓		
Glutathione peroxidase	↓		
Myosin light polypeptide	↓		
Protein kinase C epsilon	↑		
70 kDa heat-shock-like protein	↑		
Centrosomal protein CG-NAP	↑		
Annexin A2	↑		
Glyceraldehyde-3-phosphate dehydrogenases	↑		
Carbonic anhydrase 3	↑	L5 spinal nerve ligation	[8]
Creatine kinase muscle-type	↑		
β-enolase	↑		
Tropomyosin-2β	↑		
Pericollapsin response mediator protein-2	↓	partial sciatic nerve ligation	[88]
Neurotrophin-inducible protein VGF	↑	Spinal nerve ligation & Complete Freund's adjuvant-induced inflammation	[89]