Review

Unlocking Pain Therapeutics: How to Find the Right Target and Treatment Approach

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Unlocking Pain Therapeutics: How to Find the Right Target and Treatment Approach

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Abstract:

The approval of the selective NaV1.8 inhibitor Suzetrigine for acute pain has renewed optimism for developing novel analgesics, yet the clinical failure of its successor VX993 highlights the persistent difficulty of translating promising pain targets into effective therapies. This review examines why progress has been limited and how modern human-centered approaches can reshape pain-drug discovery. Human genetic studies from large biobanks demonstrate that genetically supported targets have a higher likelihood of clinical success. However, for pain, the relationship between genetic association and therapeutic efficacy is complex. Rare mutations in NaV1.7 and NaV1.8 strongly validate these channels as valid pain targets, yet common-variant studies reveal little association with chronic pain risk, underscoring a polygenic and pathway-level architecture rather than single-gene causation. Human transcriptomic atlases of dorsal root ganglia (DRG) reveal extensive redundancy across NaV channel isoforms, helping explain the modest efficacy of selective NaV1.8 inhibition and pointing toward the need for multi-target or pathway-wide approaches. Multiomic analyses in osteoarthritis highlight additional pain-generating mechanisms, including synovial inflammation, neuroimmune interactions, metabolic dysregulation, and osteoclast activity, along with the involvement of specific nociceptor subtypes. Human DRG electrophysiology and PK/PD modeling show that Suzetrigine achieves high NaV1.8 target engagement yet cannot fully silence nociceptors, and that central not solely peripheral NaV1.8 channel blockade may be required for robust analgesia. This helps explain the failures of peripherally restricted NaV1.7, NaV1.8 and TRPA1 channel blockers. Despite limitations, animal models remain essential for capturing integrated physiological responses and active drug metabolites not evident in vitro. Together, these findings support a more rigorous framework for target validation, integrating human genetics, multiomics, electrophysiology, and translational pharmacology to guide the development of next generation of pain therapeutics.

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1. Introduction

The approval of the selective NaV1.8 channel blocker Suzetrigine for acute pain treatment in 2025 marked a major milestone in the long quest to develop novel pain-relieving drugs [1,2]. This success raised hopes that more new pain drugs, targets, and novel modalities would soon follow. However, looking back, many once-promising targets never reached clinical application.

Adding to the complexity, Vertex, the company behind Suzetrigine, recently announced that its next-generation NaV1.8 blocker, VX993, failed to demonstrate clinical analgesia in acute pain [3]. This raises two critical questions:

- Why did VX993 fail?
- Why is developing new pain drugs so challenging?

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2. Human Genetic insight From Rare and Common Gene Variants

Pharmaceutical companies are increasingly drawing on large-scale human genetic resources such as the UK Biobank, the Million Veteran Program and FinnGen in hopes that directly linking a pain target to a pain phenotype will boost the probability of clinical success [4–5]. Recent estimates indicate that genetically supported targets can more than double the likelihood that a drug will ultimately reach patients [6]. Yet, for pain specifically, a similarly comprehensive analysis of genetics and novel pain therapeutics has not been published.

Target selection remains the single most critical decision in any drug discovery program. As such, all evidence that can increase the probability of success or reduce the risk of costly failure is highly valuable. Human genetic data is particularly powerful in this regard, offering an early window into potential efficacy as well as unwanted safety liabilities.

However, several high profile disappointments, most notably NaV1.7, NGF, and TRPA1, demonstrate that even strong genetic support does not guarantee successful translation into effective pain treatments. Canonical sodium channel targets such as NaV1.7 (SCN9A) and NaV1.8 (SCN10A) derive their validation largely from rare variants: gain of function mutations that increase pain and loss of function mutations that lead to pain insensitivity. These extreme phenotypes provide compelling evidence for their central role in nociception.

Curiously, some NaV1.7 variants previously thought to be pain causing are relatively common in UK Biobank genome wide association studies but show no increased risk of chronic or neuropathic pain. Population-level prescribing patterns also reveal no elevation in the use of opioid or anti neuropathic pain medications in carriers [7]. These findings suggest that a single NaV1.7 gain of function variant may not be sufficient to drive pain in the general population.

Overall, emerging genetic evidence points toward a more intricate architecture of chronic pain. Rather than being driven by single variants, pain risk likely arises from the combined influence of many common variants that confer broad polygenic susceptibility, alongside rare variants that exert large, sometimes decisive, effects. Increasingly, studies show convergence between these two classes of genetic contributors [8].

3. Human Transcriptomics

Transcriptomics, the study of all RNA molecules in a cell or tissue helps reveal gene expression patterns under different conditions. Recent transcriptomic analyses of human dorsal root ganglion (DRG) neurons and non-neuronal cells have produced a harmonized DRG atlases, now freely available online [9–11]. This enables detailed exploration of gene expression in specific sensory neuron subtypes and across all DRG cell types. However, data from healthy individuals alone provide a limited view, as only comparisons between healthy and diseased states can reveal genes that are differentially regulated in neuronal and non-neuronal pain pathways. It is likely that RNAseq data from diseased and well-phenotyped cohorts of human DRGs will be published in the near future.

However, challenges remain:

- mRNA levels do not always correlate with protein abundance or localization.
- Protein interactions within polarized sensory neurons are still poorly understood.

One key finding is the broad expression of multiple NaV channel subtypes NaV1.1, NaV1.2, NaV1.3, NaV1.5, NaV1.6, NaV1.7, NaV1.8, and NaV1.9 in pain-sensing neurons. This suggests redundancy, meaning multiple channels can perform similar functions, allowing compensation if one is blocked. Electrophysiologically, all NaV channels are more or less specialized but all of them can fire action potentials upon depolarization. Previously, NaV1.7 and NaV1.8 were thought to dominate axonal conduction. Redundancy may explain Suzetrigine's limited analgesic efficacy and suggests that multi-target NaV channel inhibition could improve outcomes [12,13].

4. Multiomic Insight from Common Diseases

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A growing body of epidemiological evidence indicates that obesity is a major driver of the global increase in osteoarthritis (OA) [14]. Excess body weight does more than overload the joint surface; it also increases mechanical stress on tendons and ligaments, structures increasingly recognized as contributors to inflammatory arthritis [15].

These insights raise a timely and important question: Could obesity-induced low grade inflammation and metabolic dysregulation within tendons, ligaments, and the synovium, the metabolically active lubricating membrane lining joint capsules and tendon sheaths, initiate and sustain chronic OA pain?

This hypothesis is strengthened by the observation that synovial inflammation is highly prevalent across all stages of OA, from early disease to advanced degeneration [16]. Together, these findings point toward a model in which obesity not only increases mechanical joint loading but also creates a pro inflammatory, metabolically altered microenvironment that may accelerate OA progression and amplify pain.

Multiomic analyses of human diseased tissues may offer a powerful route to identifying novel pain targets for highly prevalent diseases like OA. By integrating cell type–specific transcriptomic, proteomic, and metabolomic data, it may be possible to pinpoint the biological processes that both initiate and maintain pain.

Recent human multiomic and genetic studies have begun to map these mechanisms. One large scale analysis identified eight major biological processes implicated in OA pathogenesis, including the circadian clock, glial-related pathways, and TGFβ, FGF, WNT, BMP and retinoic acid signaling, as well as extracellular matrix organization [17]. Complementary work has shown that multiple immune cell types such as dendritic cells, monocytes, macrophages, fibroblasts, and osteoclasts are enriched in OA-affected synovium [18], underscoring the importance of inflammation in joint degeneration.

Clinical evidence further underscores the central role of peripheral tissues in driving OA pain. Patients with advanced, painful OA typically experience substantial and durable pain relief following joint replacement surgery, indicating that simply removing the diseased and inflamed joint tissues is often sufficient to resolve symptoms. This strongly supports a model in which peripheral sensitization within the joint microenvironment sustains chronic OA pain.

Subchondral bone marrow lesion size has been shown to correlate with both the severity of weight-bearing pain and changes in pain intensity over time, independent of non weight bearing pain, in knee OA [19]. This relationship suggests that an increased number of osteoclasts within the affected joint may contribute not only to the formation of subchondral bone lesions but also directly to pain generation. Together, these findings emphasize the need for deeper investigation into the role of osteoclasts in the genesis of OA pain.

An important next step is understanding how joint pathology communicates with the nervous system. For example, it would be informative to know whether joint replacement alters immune-cell infiltration in dorsal root ganglia (DRG). Supporting this line of inquiry, recent work showed that systemic macrophage depletion reduced pro inflammatory macrophages in the DRG and alleviated pain behaviors in a surgically induced OA model without affecting joint damage [20]. These findings highlight immune–neuron interactions as potential drivers of chronic OA pain.

Intriguingly, metformin use in patients with type 2 diabetes has been associated with reduced risk of total joint replacement in OA patients, hinting at a protective effect [21]. Blocking NaV1.7 in chondrocytes has been shown to be chondroprotective [22], and earlier work demonstrated that metformin downregulates NaV1.7 expression via the ubiquitin ligase NEDD4-2 [23]. Together, these results suggest that metformin may partly help protect chondrocytes through reduced NaV1.7 channel expression.

Because disease modification alone is insufficient for regulatory approval and meaningful pain relief remains essential, the critical challenge is to identify the biological processes that specifically drive OA pain, rather than OA pathology in general. A recent human multi omic study integrating transcriptomic and genetic data provides important clues: the peptidergic C fiber subtype

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hPEP.PIEZO and the Aδ low threshold mechanoreceptor subtype hAd.LTMR appear to contribute to joint pain and knee pain, respectively [24]. Notably, both neuronal subtypes are specialized for detecting mechanical pain, aligning well with the predominantly mechanical nature of OA symptoms.

Additional evidence comes from clinical studies showing that intra articular administration of TRPV1 agonists provides significant pain relief in OA patients [25]. This observation is consistent with the expression of the TRPV1 ion channel in peptidergic C-fiber sensory neurons, further supporting the idea that targeting specific nociceptor subtypes may offer a path to effective analgesia in OA.

5. Human In Vitro Electrophysiology, Target Engagement and Clinical Analgesia

Access to human dorsal root ganglion (DRG) neurons from organ donors has significantly advanced pain research. These sensory neurons can now be obtained either from deceased organ donors or from patients undergoing specific surgical procedures [26].

The whole cell patch clamp technique enables measurement of ion channel currents and real time membrane voltage in live cells [27]. In voltage clamp recordings from human DRG neurons, suzetrigine was shown to block human NaV1.8 channels with an IC_{50} of 0.68 nM [2]. In current clamp recordings, the selective NaV1.8 blocker suzetrigine reduced repetitive action potential firing in a dose dependent manner during depolarization, but did not completely eliminate it. Remarkably, neurons were still capable of firing action potentials even when more than 99% of NaV1.8 channels were inhibited [12]. Dynamic clamp studies have shown that reducing NaV1.8 conductance substantially alters DRG neuron excitability, both under baseline conditions and in neurons rendered hyperexcitable by a NaV1.7 mutation associated with neuropathic pain. Notably, a subset of nociceptors displayed only a weak response to NaV1.8 subtraction, suggesting that additional ion channels must be targeted to achieve comprehensive pain relief [13].

Pharmacodynamic–pharmacokinetic (PK) correlations for suzetrigine can be established using PK studies conducted in animal models as well as in human volunteers and patients. These studies measure total and unbound suzetrigine concentrations in plasma, DRG tissue, and brain. An integrated FDA review document indicates that therapeutic doses of suzetrigine block approximately 90–95% of NaV1.8 channels, demonstrating a high degree of in vivo target engagement [1]. Target engagement refers to the extent to which a drug interacts with its intended molecular target in a living biological system.

These findings raise the possibility that achieving even closer to 99% NaV1.8 inhibition at clinically relevant exposures may reveal the full analgesic potential of NaV1.8 blockade. However, achieving such high levels of inhibition would likely require higher doses, potentially narrowing the therapeutic safety margin even if it results in stronger pain relief.

It is noteworthy that VX993, a follower compound to suzetrigine, appears to have been optimized for improved solubility while maintaining high potency and selectivity for NaV1.8. In general, increased solubility can be expected to achieve higher target engagement in vivo. Despite this, VX993 did not produce statistically significant relief of acute pain in clinical testing [3]. Improved solubility typically enhances absorption, distribution and excretion but reduces metabolism (ADME) properties relative to its predecessor. However, a potential drawback is that increased solubility may reduce penetration into the central nervous system (CNS) and spinal cord.

P glycoprotein (P gp) is an important factor in this context, as it limits CNS exposure for many drugs. At the blood–brain barrier, P gp actively transports small molecule xenobiotics out of endothelial cells and back into the bloodstream, creating an “efflux barrier” that restricts passive diffusion into the brain.

6. Species Differences in NaV1.8 Current Density and NaV Blockade Site of Action

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An additional complication for drawing conclusions from in vivo studies performed in rat: when human NaV1.8 is expressed in rat NaV1.8 knockout DRG neurons, its peak current is about 2 fold larger, action potential width is about ~3 times longer and show increased firing frequencies compared with rat DRG neurons [32]. This suggests that human NaV1.8 requires more substantial inhibition to achieve analgesia.

Finally, the site of action matters. Pharmacokinetic data show that suzetrigine readily penetrates the CNS, achieving comparable concentrations in the brain and plasma [1]. This distribution strongly suggests that suzetrigine can access and block NaV1.8 channels not only in peripheral axons but also in the central axons of these neurons, enabling balanced, pathway wide NaV1.8 inhibition.

This distinction is critical. If NaV1.8 blockade is restricted to peripheral nerve endings, axons, or even the sensory neuron soma, NaV1.8 dependent action potentials can re emerge once sufficiently strong depolarization reaches the central axons, allowing pain signals to continue propagating. In contrast, a compound like suzetrigine, capable of inhibiting NaV1.8 across the entire nociceptive pathway, has the potential to achieve a far more complete and durable suppression of pain signalling (Fig. 1).

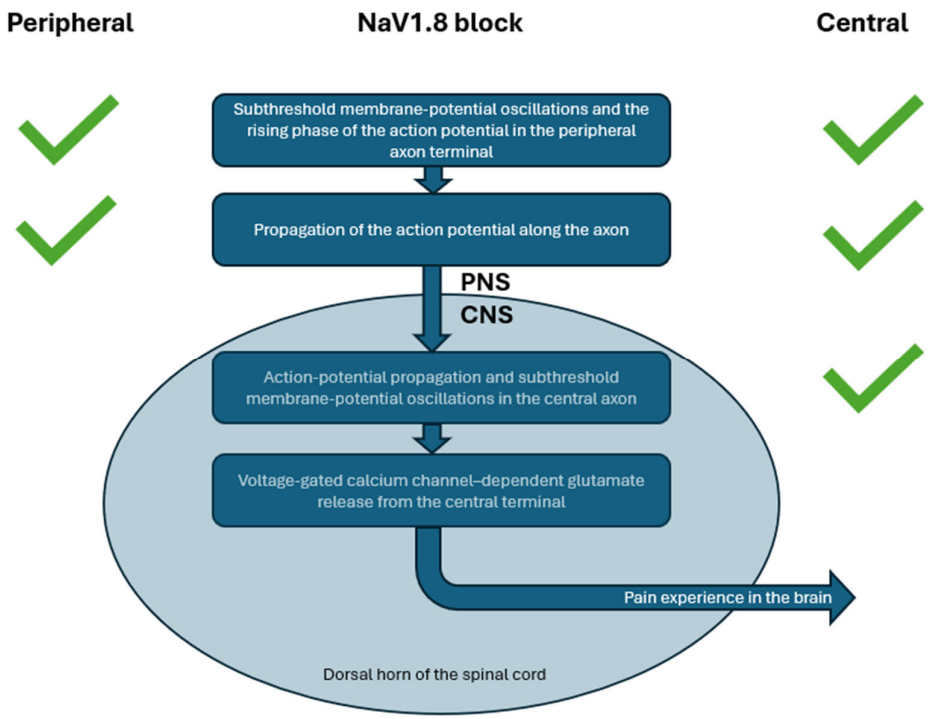

Figure 1. Differences Between Peripheral and Central NaV1.8 Block. A peripherally restricted NaV1.8 blocker reduces subthreshold membrane potential oscillations and action potential initiation in peripheral nerve terminals. It also limits action potential propagation along peripheral axons. A centrally acting NaV1.8 blocker, by contrast, produces a broader inhibition profile. It blocks NaV1.8-dependent action potential propagation and subthreshold oscillations within central axons as well. Importantly, peripheral NaV1.8 block has no effect beyond the PNS–CNS junction. The passive electrotonic spread that reaches into the CNS is too weak to depolarize central terminals enough to open voltage-gated calcium channels. Without sufficient calcium entry, the calcium-dependent mechanisms that drive glutamate release in central synaptic terminals cannot occur. Action potentials are required to generate the level of depolarization needed to activate these channels and initiate neurotransmitter release.

A selective NaV1.7 blocker, PF 05089771 developed by Pfizer, failed to demonstrate clinically meaningful analgesia in patients with painful diabetic neuropathy [33]. PF 05089771 carries a positive

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charge at physiological pH, a property known to limit CNS penetration and likely contributing to its lack of efficacy in humans.

However, new evidence challenges the long held assumption that peripheral NaV1.7 block alone is sufficient for pain relief. A recent study showed that intrathecal administration of PF 05089771 produced robust analgesia across multiple animal pain models [34]. This finding highlights the importance of drug access to central NaV1.7 channels.

Further supporting this concept, intrathecal delivery of a NaV1.7 antisense oligonucleotide resulted in significant pain relief along with a marked reduction of NaV1.7 protein in the dorsal horn, DRG soma, and central axons but not in peripheral nerve fibers [35]. These data strongly support the hypothesis that central inhibition of NaV1.7 is both necessary and sufficient to produce analgesia, whereas peripherally restricted compounds may be inherently limited.

Clinical and preclinical data from suzetrigine and PF 05089771 help explain why VX993 failed in the acute pain clinical trial. VX993 was likely designed to improve solubility allowing its use as an intravenous formulation. However, greater solubility is likely to reduce BBB penetration into the CNS. I propose the hypothesis that limited CNS exposure by VX993 contributed to its lack of analgesic efficacy.

7. Why peripheral TRPA1 Blocker Did not Provide Pain Relief?

TRPA1 is a nonselective cation channel expressed in pain sensing neurons [36]. It is activated by a wide range of known pain mediators [37], and activation in human volunteers reliably produces pain [38]. Moreover, gain of function variants in the TRPA1 gene are genetically associated with increased pain sensitivity in humans [39–40].

Despite extensive drug discovery efforts to develop potent, selective, and drug like TRPA1 antagonists, clinical translation has been challenging. Eli Lilly evaluated a peripherally restricted TRPA1 antagonist, LY3526318, in patients with diabetic neuropathic pain, osteoarthritis pain, and low back pain [41]. Unfortunately, LY3526318 did not provide meaningful pain relief [42].

However, a growing body of preclinical evidence suggests that peripheral blockade alone may not be sufficient. TRPA1 is also expressed in the central axons of peripheral sensory neurons, where its activation amplifies nociceptive signalling [43–44]. Importantly, intrathecal administration of a small dose of a selective TRPA1 antagonist, one incapable of blocking peripheral TRPA1, produced robust analgesia in animal models [45–46].

Initial Northern blot analysis of bulk RNA suggested that TRPA1 expression was restricted to the peripheral nervous system [36]. In contrast, recent single cell RNA seq analyses reveal TRPA1 expression in the human brain and spinal cord [47]. In animal studies, TRPA1 activation within the amygdala in the brain has been shown to enhance both nociceptive responses and the affective dimension of pain [48].

Taken together, these findings strongly suggest that the full analgesic potential of TRPA1 antagonism remains untested in clinical trials. A compound capable of blocking TRPA1 in both peripheral and central axons of pain sensing neurons and in the CNS may be required to unlock the true therapeutic benefit of this target.

8. Animal Models

Animal models have historically played a critical role in the development of novel painkillers [28]. Only an awake animal can exhibit pain-like behaviours, enabling in vivo assessment of potential analgesic efficacy. However, reproducibility of the in vivo results is still a major issue. This has led to requests from scientific journals for more transparent reporting of data, use of blinding and randomization and other good practices to avoid bias. An interesting new development is the use of machine vision and machine learning to automatically extract and quantify behavioral features that capture the internal pain state of rodents in multiple pain models [29], and a machine learning tool

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with light based image analysis for automatic classification of 3D pain behaviours [30], which hopefully could provide unbiased behavioural data with minimal human interference.

9. Why Animal Studies Still Matter

Today, one of the main reasons for conducting in vivo animal studies is to gain insight into target engagement and establish pharmacokinetic/pharmacodynamic (PK/PD) correlations. In simple terms: How much of the target protein needs to be blocked in vivo based on the in vitro IC_{50} value?

The development of suzetrigine illustrates several key issues. Suzetrigine is a highly potent and selective NaV1.8 blocker. According to FDA documentation, suzetrigine was advanced to clinical trials without prior animal efficacy testing, though pharmacokinetics and toxicology were studied in animals. Why [1]?

A recent study showed robust efficacy of suzetrigine in a mouse neuropathic pain model, despite the fact that suzetrigine blocks mouse NaV1.8 nearly 500 times less potently than human NaV1.8 [31]. This implies that achieving efficacy in mice would require doses hundreds of times lower than those used in humans. Clearly, a mouse PK–PD study is not ideal for human dose prediction.

Vertex made a bold decision to proceed directly to human trials without animal efficacy support, relying instead on pharmacokinetic modelling to predict human exposure and safety margins. FDA data now confirm that NaV1.8 is inhibited by ~95% at therapeutic doses in humans. This sheds light on the mouse data:

- In mice, analgesia occurred at exposures well below the IC_{50}, whereas in humans, nearly complete NaV1.8 blockade was required.
- This highlights the danger of drawing conclusions from animal efficacy studies without accounting for free, unbound drug concentrations and species-specific pharmacology.

One key reason animal models remain indispensable is their ability to capture the full, integrated physiological response to drug exposure across intended molecular targets, biochemical pathways, neuronal circuits, and anatomical sites that collectively shape pain processing in vivo. This systems-level response simply cannot be inferred from in vitro studies, which isolate individual components and therefore miss emergent network effects.

Moreover, some drugs are converted into pharmacologically active metabolites in the body. These metabolites can significantly amplify or modify the net analgesic effect, and their contribution can only be accurately assessed through in vivo experimentation.

10. Conclusions

Human genetic insights from large scale biobanks continue to offer a powerful and unbiased route for discovering new pain targets. As these datasets expand, it is increasingly likely that the next wave of genetically supported pain targets will emerge not only from direct associations with pain phenotypes, but also from genes embedded in biologically relevant pathways connected to pain phenotypes through genetic linkage. The primary bottleneck is no longer in generating genetic insights, but in transforming those insights into actionable and therapeutically meaningful targets.

Crucially, incorporating genetic data from individuals with more diverse ancestries will substantially increase the statistical power to detect previously overlooked pain driving genes [5]. This broader genetic representation strengthens confidence in target relevance and enhances the generalizability of findings.

At the same time, advances in multi omics, particularly RNA seq, allow researchers to map gene expression across the extended pain pathway, identifying targets enriched not only in sensory neurons but also in key non neuronal cell types that modulate nociception. The goal remains clear: to prioritize targets selectively enriched in these pain relevant circuits while minimizing the risk of unwanted effects in unrelated tissues.

About 98–99% of human genetic variation occurs in non coding regions of the genome, which include key regulatory elements such as enhancers, promoters, and transcription factor–binding sites

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[49–50]. Many quantitative trait loci (QTLs) are genomic regions whose DNA variants influence continuously varying traits. QTLs act by regulating gene and protein expression rather than altering protein structure. Because of this, high resolution quantitative proteomic analyses of healthy and diseased human tissues provide a powerful opportunity to identify the proteins and molecular pathways that drive and maintain chronic pain.

The rapid emergence of new therapeutic modalities, ranging from biologics, antibody drug conjugates, PROTACs and molecular glues to RNA targeting agents, opens unprecedented opportunities to modulate target protein function, expression or mRNA within the extended pain pathway that were previously inaccessible with small molecules alone.

11. Future Directions

Ultimately, even as advanced genomic, transcriptomic, and proteomic tools continue to refine our understanding of pain biology, true progress depends on assembling a rigorous and persuasive pain target validation package (Fig. 2) [51]. Such a framework must clearly define where the therapeutic is expected to act, establish why that anatomical or molecular site is essential to pain processing, and demonstrate how modulating the target is likely to produce clinically meaningful analgesia in humans. Equally crucial is determining whether strong human genetic evidence supports the candidate protein or the regulatory pathways that govern its activity or expression as a causal contributor to pain. Together, these elements provide the foundation needed to bridge fundamental discovery with translational success and to advance the next generation of pain therapeutics.

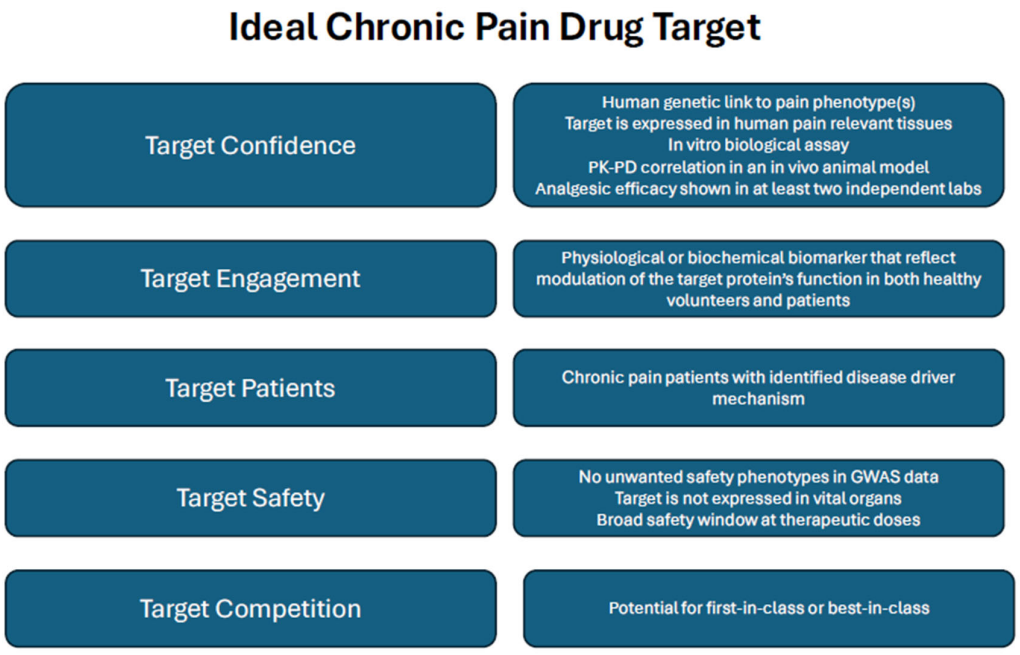

Figure 2. A five-dimensional framework for an ideal chronic pain drug target, adapted from Morgan et al. [51]. At the outset of a drug discovery project, several knowledge gaps typically remain. By the time the project is ready to nominate a candidate compound, most dimensions of the framework have been investigated and are supported by experimental data.

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