Opportunity

Treatment options for chronic low back pain and chronic pain in general are quite limited. The opioid crisis has led to a sharp reduction of the utilization such therapies for chronic pain. Better understanding of the risks of nonsteroidal anti-inflammatory drugs including renal failure, peptic ulcer disease, and myocardial infarction has limited their utility for chronic pain management as well.

Less toxic and non-addictive therapies are desperately needed for patients who suffer from chronic pain.

PTCI solution

PTCI was initially founded to identify better compounds for topical analgesia to treat acute and chronic pain. The founders identified a market need illustrated by a combination of factors including the prevalence of chronic pain, the commercial success of Lidoderm® patches, and the need for alternative pain treatments created by the opioid crisis.

Of note is that a large majority of Lidoderm® prescriptions were written for the off-label uses of chronic low back pain. Endo Pharmaceuticals paid a $192.7 million fine to the United States federal government to resolve off-label marketing claims, most related to promotion for low back pain.

The evidence for clinical utility of topical lidocaine preparations for indications other than postherpetic neuralgia is mixed. Several small uncontrolled studies have suggested significant improvement with topical lidocaine for chronic low back pain. There is one small randomized controlled trial for chronic low back pain that did not show clear benefit over placebo, although the placebo effect was unusually large.

The amide family of local anesthetics has been used for decades with no fundamental changes or updates to the agents used clinically. Knowing the above, the founders of PTCI sought to develop a better topical analgesic in terms of both efficacy and tolerability.

Advances in understanding of the nine human voltage-gated sodium channels ($Na_v1.1$-1.9) allowed investigators to model the channels of interest virtually while also modeling candidate molecule interactions with the various sodium channels. For example, activity at $Na_v1.7$ and $Na_v1.9$ would be expected to have analgesic effects while activity at the $Na_v1.5$ channel would affect cardiac conduction.

The team partnered with Southwest Research Institute in San Antonio, Texas, for the initial virtual modeling of the receptors and a docking and scoring assessment of a

panel of candidate therapeutic molecules. After selecting a group of molecules, the team then performed patch-clamp in vitro testing to assess specificity of each molecule for individual sodium channel isoforms. Further testing was conducted to assess both pKa and lipophilicity. While the initial impetus for development was a better topical agent, the investigators realized that improving injectable anesthetic agents would be useful as well.

The result of the above work is a bank of molecules, each of which has been assessed for voltage-gated sodium channel subunit specificity, molecule lipophilicity, and pKa. PTCI then selected eight candidate molecules with the most potential for clinical efficacy and tolerability. Notably these molecules vary in their characteristics; higher lipophilicity, for example, would be preferred for most injectable treatments to ensure tissue penetration but lower lipophilicity would be preferred for topical agents treating more superficial symptoms. Of interest is that a topical amide agent with high lipophilicity would heretofore have been avoided because of the potential for excess systemic absorption and toxicity. Limiting $Na_v1.5$ effects, though, would allow consideration of such an agent for topical and perhaps even systemic administration as more systemic absorption would not mean increased potential for cardiac toxicity.

Confirming the potential utility and safety of newly designed sodium channel blockers is VX-548, an orally administered product from Vertex pharmaceuticals. Specifically targeting $Na_v1.8$, VX-548 is now in phase three studies for various types of pain.

PTCI now has obtained nine granted US patents for all the molecules of interest. Patents are pending in other countries. At this point, the molecules are ready for further development. Of import is that optimization of functional groups on the molecules has intentionally been limited to only one end of each molecule, thereby leaving room for further development on the other end if desired.

In addition, one continuation patent application is still pending in the United States, allowing any further molecule development a straightforward path to additional patent protection.

This bank of patents covers a broad swath of lidocaine analogues including further derivatives of the candidate molecules. Obtaining these patents would allow a pharmaceutical company to explore candidate molecules for use in the anesthetic space (including topical, injectable, and oral routes of administration) while being assured of patent protection.

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