The quest for non-addictive chronic pain therapies

Chronic pain is a complex and distressing condition that affects over 1.5 billion people globally, with pain and pain-related diseases being the leading cause of disability and disease burden. In the UK alone, it has been estimated that about 8 million adults experience moderate to severe pain for more than six months. In Europe, around 1 in 5 people are thought to suffer from chronic pain, with the direct and indirect costs being equivalent to around 1.5% of Europe's annual gross domestic product (GDP). In the US, chronic pain has been reported to cost in the range of $560 billion to $635 billion per year, comprised of direct healthcare, missed hours and days of work, and lower wages.

Existing treatments for chronic pain include opioids, nonsteroidal and anti-inflammatory drugs (NSAIDs) and physical therapy, although all only provide partial relief and at the cost of known side effects and risks. A 78% risk of an adverse reaction to opioids has been estimated and a 7.5% risk of a severe adverse event[1]. In the US, around 21-29% of patients misuse opioids prescribed to treat chronic pain, and about 8-12% develop a disorder related to opioid use[2], with opioids responsible for 75.4% of all drug overdose deaths as reported in a 12-month period[3]. An increase in opioid use has also been found in some parts of Europe in recent years.

With such a global healthcare burden, and a lack of available and effective non-addictive options to treat chronic pain, it is clear that efficacious, safe, and non-addictive pain therapeutics are urgently needed.

Several ion channels and G protein-coupled receptors (GPCRs) have been implicated in an abnormally heightened sensitivity to pain (hyperalgesia and allodynia). Selective targeting of these ion channels and GPCRs could pave the way for more effective pain therapeutics. In particular, ion channels such as Nav1.7 and Nav1.8, which are supported by robust genetic validation, have commanded significant attention from drug developers in the last decade. Gain-of-function mutations in these channels have been shown to result in hyperalgesia or allodynia in humans, while loss-of-function mutations can cause congenital insensitivity to pain.

However, selectively targeting ion channels such as Nav1.7 and Nav1.8 with small molecules is tricky, as they are members of a family of highly homologous ion channels (Nav1.1 to Nav1.9) that are critical for other functions in the body[4]. For example, unwanted cross-reactivity of a Nav1.7 or Nav1.8 targeting drug candidate to Nav1.4 can cause paralysis as it controls skeletal muscle excitability. Beyond the challenges associated with selectivity, achieving efficacy may also depend on sustained inhibition of most of the misfiring ion channels. This necessitates a prolonged *in vivo* half-life or frequent dosing of the medicine, adding additional complexity to an already difficult task.

The recent results for Vertex Pharmaceuticals Inc's non-addictive small molecule Nav1.8 inhibitor, VX-548, are exciting for the pain field, with positive Phase 3 data demonstrating a significant easing of post-surgical pain compared with placebo. Unfortunately, it was also shown not to be as effective as Vicodin, an opioid-containing drug. These results highlight the significant opportunity, as well as the critical need, for the industry to continue to develop further therapeutic candidates that present effective alternatives to opioids for the treatment of chronic pain.

Antibody-based drugs are a potential answer to this need, offering high potency, selectivity, engineerability, and a long *in vivo* half-life. Compared with small molecules, engineered antibodies offer vastly superior selectivity and are well-proven therapeutically, representing six out of ten of the world's top-selling drugs. Despite these obvious advantages, including an excellent track record of clinical success, antibody discovery against ion channels and GPCRs has been very challenging. The formidable difficulty is underscored by the absence of a single monoclonal antibody in clinical trials against this specific class of protein targets. Meanwhile, there are over 1,000 clinical trials testing antibodies against various other target protein classes.

At Maxion Therapeutics we are committed to developing first-in-class and best-in-class therapeutics for previously untreatable ion-channel and GPCR-driven diseases including autoimmune diseases and chronic pain. Our KnotBody technology platform fuses miniproteins (knottins) which modulate ion channels within antibody surfaces to create a new class of fusion antibodies called KnotBodies. Natural knottins suffer from problems such as rapid removal from the blood circulation and unwanted cross-reactivity in the body, causing side effects and difficulties in manufacturing at scale. KnotBodies aim to combine the best of both components – preserving the ion channel modulating function of knottins while enjoying the optimum drug-like properties of antibodies. This includes engineerability to improve potency and selectivity as well as manufacturability and an extended half-life typical of antibodies.

By harnessing nature, this revolutionary approach integrates the power of millions of years of knottin evolution with state-of-the-art antibody engineering technologies to address targets previously off-limits to small molecules and traditional antibody approaches. Our lead programme for treating autoimmune diseases is rapidly advancing towards preclinical development with several programmes against other indications also in the pipeline. In summary, we and others across the industry remain focused on relieving the overall global healthcare burden with innovative and long-term solutions for key indications such as chronic pain.

References: 1. Els C, Jackson TD, et al, Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017 Oct 30;10(10). 2. Oelhaf RC, Del Pozo E, Azadfard M. *Opioid Toxicity*. 2023 Jul 21. In: StatPearls. 2024 Jan. 3. US Centres for Disease Control and Prevention. Drug Overdose Deaths. 2023. 4. Kingwell K. Nav1.7 withholds its pain potential. *Nat Rev Drug Discov*. 2019 Apr 8.

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