Response to letter to the Editor

To the Editor:

We would like to thank Dr. Gofeld, who raised several concerns about our article [1]. We had previously received similar remarks on our paper. Maybe it is because radiofrequency (RF) neurotomy for knee osteoarthritis is a new procedure based on nerve innervations by multiple articular branches. According to the anatomy textbook [2], several articular branches of the knee originate from the tibial and common peroneal nerves and accompany the superior medial, inferior medial, middle, superior lateral, and inferior lateral genicular arteries. The superior medial, superior lateral, and inferior medial arteries pass the medial and lateral condyle of the femur and the medial condyle of the tibia, respectively. Because RF neurotomy is based upon the identification of anatomic landmarks for nerve innervations, points of condyle can be targeted for RF neurotomy.

There have been a few reports in which articular branches of the knee joint are called the genicular nerves [3,4]. Furthermore, it is known that several articular branches pass close to the epicondyle, anatomic landmark of long bone. This was also confirmed by nerve sensory stimulation for RF neurotomy in our study. Nevertheless, several anatomic problems, such as variation and function of the articular branches, remain to be established. Clearly, additional studies are needed to confirm the pain innervation of knee osteoarthritis and the safety of RF neurotomy.

About Figure 2 in our article, this is the C-arm X-ray image for the left knee of a female subject in the supine position and with a pillow under the popliteal fossa. This image quality is so cloudy due to our old C-arm machine, and may be estimated as a normal joint. However, her left knee anteroposterior X-ray findings in a standing position (Fig. 1) showed a medial joint space narrowing with osteophytes (Kellgren-Lawrence grade 2).

We agree with Dr. Gofeld about his remark for Figure 5. We regret not providing sufficient detail in our explanation of Figure 5. In Figure 5, the left side of the picture is an image of the entire left knee with superficial dissection. The pictures on the right side of the figure are enlarged images of the left knee with deeper dissection. We selected the image of the left knee with superficial dissection because the deeper dissection image was not able to show exactly the muscles or ligaments that covered articular branches. Also, number 3 in picture A actually indicates the adipose tissue fold below the adductor magnus, not the muscle.

References

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Letter to the Editor

To the Editor

Genetic studies [3] have shown the important role that sodium channel Na1.7 (encoded by the SCN9A gene) has in human pain perception, and this protein has been targeted for the development of novel analgesics [2–5]. Several reported novel small-molecule Na1.7 inhibitor compounds are currently in clinical development. One of these compounds (PF-05089771) has been reported to demonstrate molecular selectivity for Na1.7 over certain other members of the voltage-gated sodium channel protein family [7,8].

We developed XEN402 as a potent state-dependent blocker of voltage-gated sodium channels, including nanopomol inhibition of Na1.7. In 2012 we published, in PAIN®, data from an exploratory trial studying the analgesic properties of XEN402 in patients with inherited erythromelalgia (IEM) [6]. Each of
the 4 IEM patients in this study carried a heterozygous missense mutation in the SCN9A gene, which was presumed to cause a gain of function in Na\textsubscript{v}1.7 and be causative of the resultant spontaneous or easily provoked pain from which these patients suffer. In this trial we demonstrated that XEN402 reduced the amount of pain that could be induced by a heat stimulus in these patients. The heat stimulus protocol used in this trial would not elicit a painful response in healthy subjects; the aim of the heat induction endpoint in these IEM patients was an attempt to separate and study the Na\textsubscript{v}1.7 component of their pain. We believe the reduction in the amount of heat-induced pain observed while on XEN402 treatment supports our conclusion of the ability of this compound to interact with and block Na\textsubscript{v}1.7 in IEM patients. However, given that XEN402 does have activity against other sodium channels (Na\textsubscript{v}s), we cannot exclude that some of the pharmacological activity observed is mediated through XEN402 inhibition of other Na\textsubscript{v} channels [6].

Since publication, several readers of this journal have requested additional information about XEN402, and here we supplement our initial report by presenting its structure along with IC\textsubscript{50} data generated for XEN402 against sodium channels where such data are available.

XEN402 was discovered during optimization activities conducted around the previously described spirooxindole lead compound XEN907 [1]. XEN402 is (S)-1’-[5-((trifluoromethyl)-2-furyl)methyl]spiro[furo[2,3-\text{f}]1,3]benzo-dioxole-7,3’-indol]-2(1H)-one (Fig. 1).

The potency of XEN402 for block of voltage-gated sodium channels has been studied using patch-clamp electrophysiology with cell lines that heterologously express the human isoform. XEN402 shows voltage-dependent block of sodium channels with cell lines that heterologously express the human isoform. The IC\textsubscript{50}\textsuperscript{s} derived using optimized voltage for potency for Na\textsubscript{v}1.2, Na\textsubscript{v}1.5, Na\textsubscript{v}1.6, and Na\textsubscript{v}1.7 are 601 nM, 84 nM, 173 nM, and 54 nM, respectively. The protocol used for the above sodium channels is not suitable for the study of Na\textsubscript{v}1.8 because it relies on incomplete slow inactivation at voltages that promote substantial fast inactivation, and this could not be attained for hNa\textsubscript{v}1.8. Using a modified electrophysiology protocol, the IC\textsubscript{50} for Na\textsubscript{v}1.8 is 4.8 \textmu M. We recommend caution in interpreting the potency for Na\textsubscript{v}1.8 given the change in protocol and the observation that native rat Na\textsubscript{v}1.8 has gating properties that differ from those of heterologously expressed hNa\textsubscript{v}1.8. We have not heterologously expressed Na\textsubscript{v}1.9 and thus, not measured the potency of XEN402 against this channel. It is our intention to publish more detailed information on the biophysical and electrophysiological properties of XEN402 in due course.

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