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Substance P saporin for bone cancer pain in dogs: Can man's best friend solve the lost in translation problem in analgesic development?

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Re: Brown DC, Agnello K: Intrathecal Substance P Saporin in the Dog: Efficacy in Bone Cancer pain. *Anesthesiology* 2013; XXX:XXX-XXX

AND

Wiese AJ, Rathbun M, Butt MT, Richter PJ, Osborn KG, Xu Q, Veasart SL, Steinauer JJ, Higgins D, Lappi DA, Russell B, Yaksh TL: Intrathecal substance P saporin in the dog: Distribution, safety, and spinal neurokinin-1 receptor ablation. *Anesthesiology* 2013; XXX:XXX-XXX

In the United States, cancer is the second most common cause of death and over a half million people die from cancer annually. Bone cancer pain is a common cause of pain in patients with advanced cancer and described as a combination of background, dull pain and breakthrough, severe pain (spontaneous and incident pain)¹. Breakthrough pain episodes, often unpredictable, affect many aspects of life, including mood, sleep, and physical/social activities, and are often refractory to conventional therapies, including opioids, nonsteroidal antiinflammatory drugs, bisphosphonates, and radiotherapy. These issues in human cancer patients are precisely mirrored in companion dogs. Dogs develop cancer about twice as frequently as humans. Large breeds such as Retrievers, Saint Bernards, and Great Danes have a much higher risk for bone cancer than small breeds. Dogs with bone cancer pain present with a variety of signs, including lameness, lethargy, anorexia, respiratory distress, and vocalization, and often respond poorly to conventional therapies, similar to their human counterparts. There is a real need for more effective therapies for cancer pain in both humans and their companion dogs.

In this month's *ANESTHESIOLOGY*, Brown *et al.*² demonstrate in companion dogs with chronic bone cancer pain that selective depletion of substance P receptor (neurokinin-1 receptor: NK-1R) expressing spinal neurons by the intrathecal injection of substance-P saporin (SP-SAP, 20–60 µg) reduces chronic bone cancer pain. Analgesia was cleverly and appropriately defined as the time unblinding was requested by the dog owner for adjustment of the analgesic protocol or euthanasia and the number of dogs requiring unblinding within 6 weeks of randomization. This work demonstrates not only the role of NK-1R expressing

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spinal neurons in bone cancer pain but also the advantage of humane use of veterinary patients for translational pain research.

Substance P is released in the spinal cord from sensory C-fiber afferents following peripheral nociceptive stimulation and activates second order dorsal horn nociceptive neurons, some of which project supraspinally to transmit pain. In many preclinical studies in animals NK-1R antagonists have been shown to reduce behavioral and electrophysiological responses sensitized by inflammation or nerve injury. Despite those preclinical results, NK-1R antagonists have failed to exhibit efficacy in clinical trials of a variety of chronic pain states, including postherpetic neuralgia, diabetic neuropathy, migraine, osteoarthritis, and fibromyalgia. One could argue that the lack of clinical efficacy in NK-1R antagonists in pain modulation was due to their inadequate blood-brain-barrier penetration or doses used in clinical trials. Against this argument is the observations that positron emission tomography studies confirmed that some of NK-1R antagonists, at the dose used in the clinical trials, were adequate to saturate the receptors in the brain, and that similar doses of the same drugs were shown to be effective in emesis, which requires both adequate brain penetration and a high degree of receptor blockade ³.

Why would destruction of NK1-R expressing spinal neurons work when blockade of NK1-Rs fails? An extensive basic science literature suggests that spinal dorsal horn neurons receive parallel signals from neurotransmitters and modulators that are released from the terminals of primary afferents and resident glia in the chronic pain state. This suggests that blockade of only one type of receptors in the spinal cord may be insufficient to prevent pain. Indeed, the approach of Brown *et al.* ² demonstrates clearly that the depletion of NK-1R expressing spinal dorsal horn neurons by the SP-SAP effectively reduced bone cancer pain in companion dogs. In this month's *ANESTHESIOLOGY*, an accompanying safety study in laboratory Beagle dogs ⁴ showed that intrathecal SP-SAP injection of 15 µg, a similar dose used by Brown *et al.* ², reduced dorsal but not ventral NK-1R expressing neurons at the spinal level of injection with minimal side effects whereas 150 µg of SP-SAP resulted in motor neuron toxicity. Although the safety range of intrathecal SP-SAP treatment still needs to be carefully determined, these results strongly support the rationale for the development of SP-SAP or agents which target a similar strategy as potential therapies for chronic pain. It should be noted that intrathecal SP-SAP will be tested in cancer pain patients (NCT01875432). We are looking forward to results of this clinical study.

Pain research has been stuck in "Lost in Translation". This comes from the limited success in pain research to translate basic science results into new, effective, and safe treatments for pain in humans. A famous example of "Lost in Translation" is the failure of NK-1R antagonists, mentioned above, which showed high profile efficacy in various animal models of pain but failed to show clinical efficacy in humans. Most laboratory studies are performed only in rodents, using reflex withdrawal measures to reflect one aspect of pain behavior, and this may be a major reason for "Lost in Translation". Although excellent discussions and reviews of the predictive validity of rodent models of pain can be found in many journals, books, and websites, one can argue that current pain models and behavioral assays in rodents have often failed to predict clinical efficacy of drugs in humans. We also need to consider the fact that many negative preclinical data of drug efficacy are likely unpublished or unrecognized. So should we wait for a new rodent pain model or assay? The answer is No! The current article demonstrates the possibility of companion dog population as a novel additional step in validating drug efficacy prior to introduction of drugs in costly and potentially harmful trials in humans. Unlike rodent models of pain, companion dogs develop chronic pain from natural causes such as cancer and arthritis with pain frequency and intensity increasing over weeks or months, reasonable time-frames to evaluate effectiveness of test treatments. As for the behavioral assessments, dog's daytime activity can be

measured by the activity meter, behavioral presentation and changes can be monitored and scored on the pain inventory by the owner who shares physical and social environments with dogs, and clinical signs of pain can be diagnosed by the veterinarian. Although there is the possible bias in the owner's observation, behavioral assessments in dogs resemble those in human, especially, pediatric patients and do not involve any stressful stimuli, which are used in most behavioral tests in rodent pain models. Dogs have been living with humans as sentinels, assistants, or friends for over 10,000 yr. Now dogs also show their potential in translational pain research. I strongly propose organizing translational research teams of those in basic science, veterinary medicine, and human medicine to solve "Lost in Translation" in pain.

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