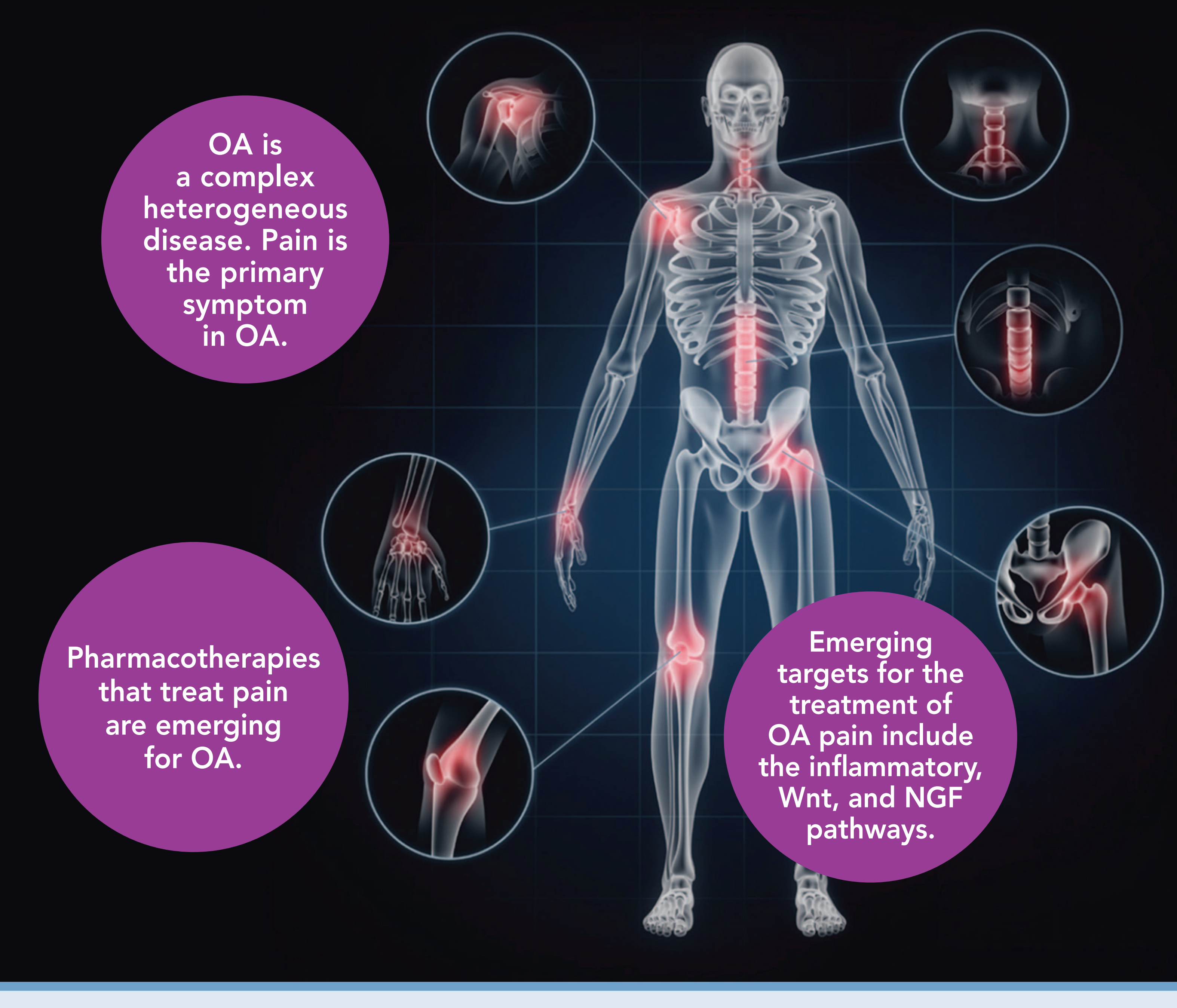
OSTEOARTHRITIS MEDICATIONS

Mechanisms of Action and Emerging Treatment Options

CLINICAL PEARLS



Evolving Approaches to Osteoarthritis Pain Management

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and often leads to disability. Traditional management treated symptoms, but did not address the underlying disease process. As our understanding of the pathophysiology of the disease advances, pharmacotherapies that target pain are emerging.

OA AFFECTS 300 million worldwide[1]

Emerging Treatment Targets

1

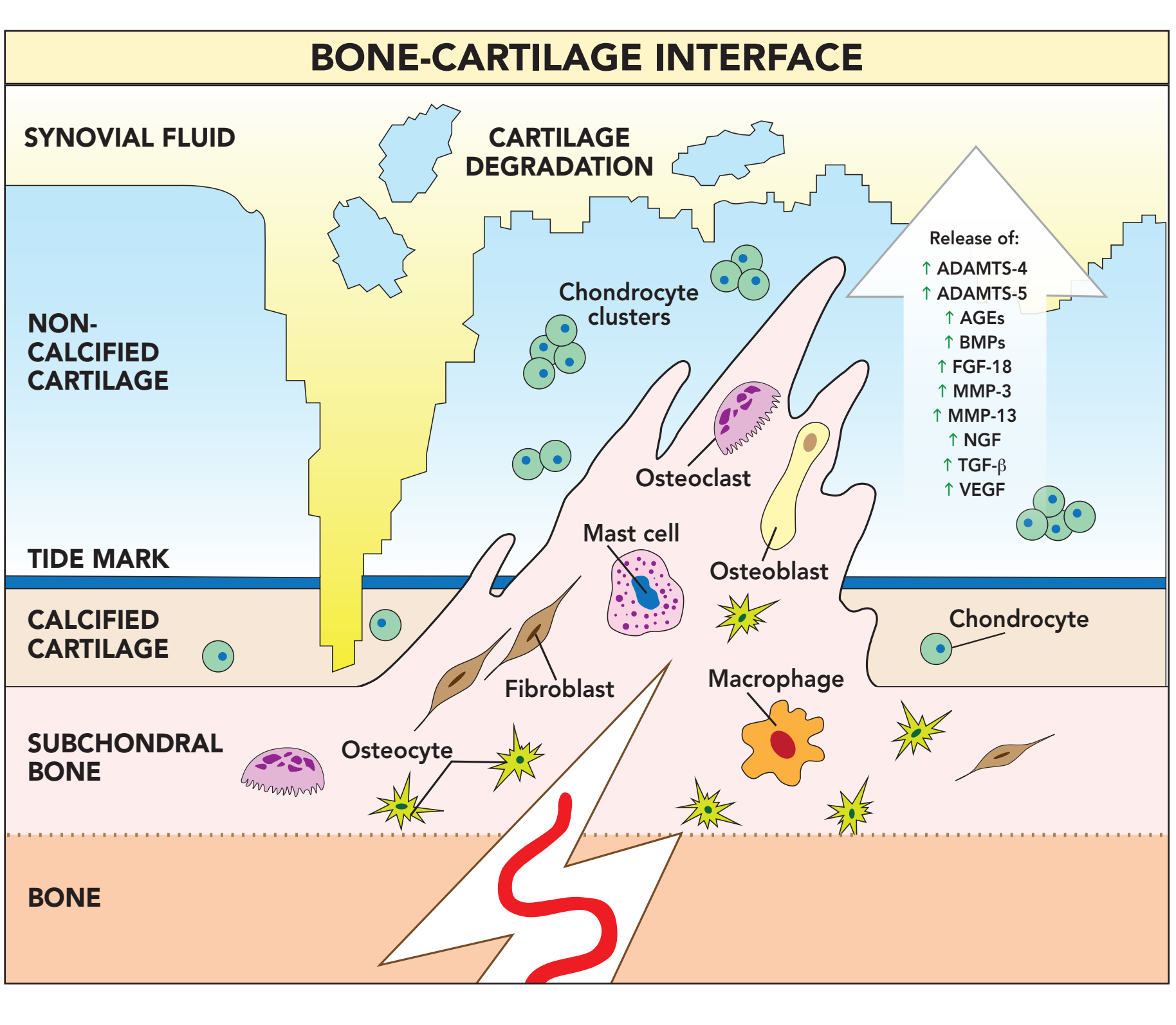
Inflammation in OA

It has been hypothesized that the inflammatory process in OA is a result of a combination of pathological processes.

OA develops as a result of changes in the synovial joint. Specifically, osteoblasts, osteoclasts, osteocytes, fibroblasts, macrophages, and mast cells from the subchondral bone invade the calcified cartilage and the non-calcified cartilage, via microfractures in the bone-cartilage interface.

This causes a disruption of the osteochondral junction and the release of ADAMTS-4, ADAMTS-5, AGEs, BMPs, FGF-18, MMP-3, MMP-13, NGF, TGF-β, and VEGF.

Inflammation and swelling occurs in the synovium, which results in peripheral sensitization.



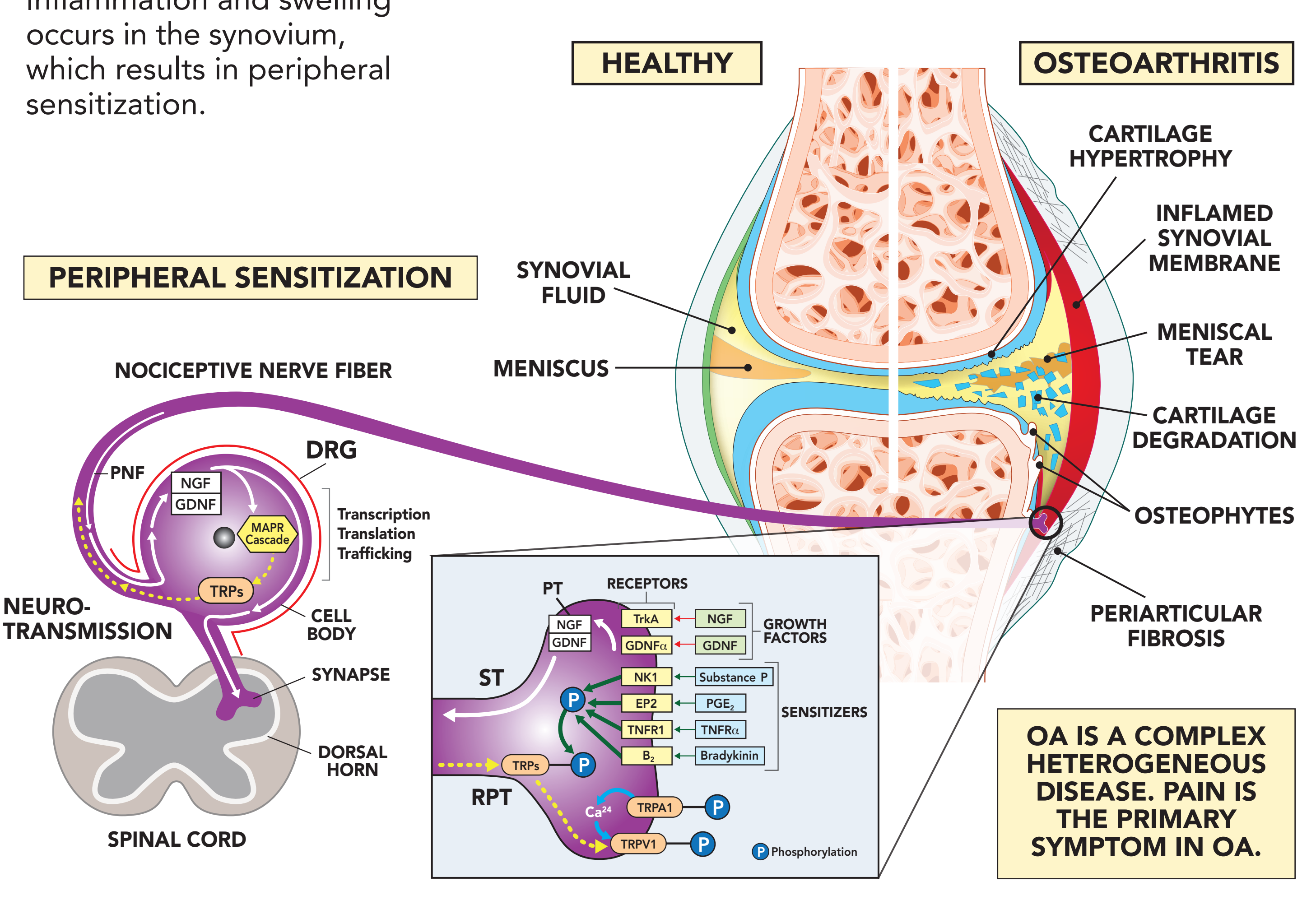


Figure adapted from reference 5.

AGE: Advanced glycation end product. BMP: bone morphogenetic protein; DRG: dorsal root ganglion; EP2: prostaglandin E2 receptor 2; FGF: fibroblast growth factor; GDNF: glial cell line-derived neurotrophic factor; MMP: matrix metalloproteinases; NGF: nerve growth factor; PGE2: prostaglandin E2; PNF: proprioceptive neuromuscular facilitation; PT: Peripheral terminal. RPT: Reducing pain threshold. ST: Signal transduction. TGF: tumor growth factor; TNFR: tumor necrosis factor receptor; TRK A: tropomyosin receptor kinase A; TRP(A): Transient receptor potential cation channel A. TRPV: transient receptor potential vanilloid; VEGF: vascular endothelial growth factor.

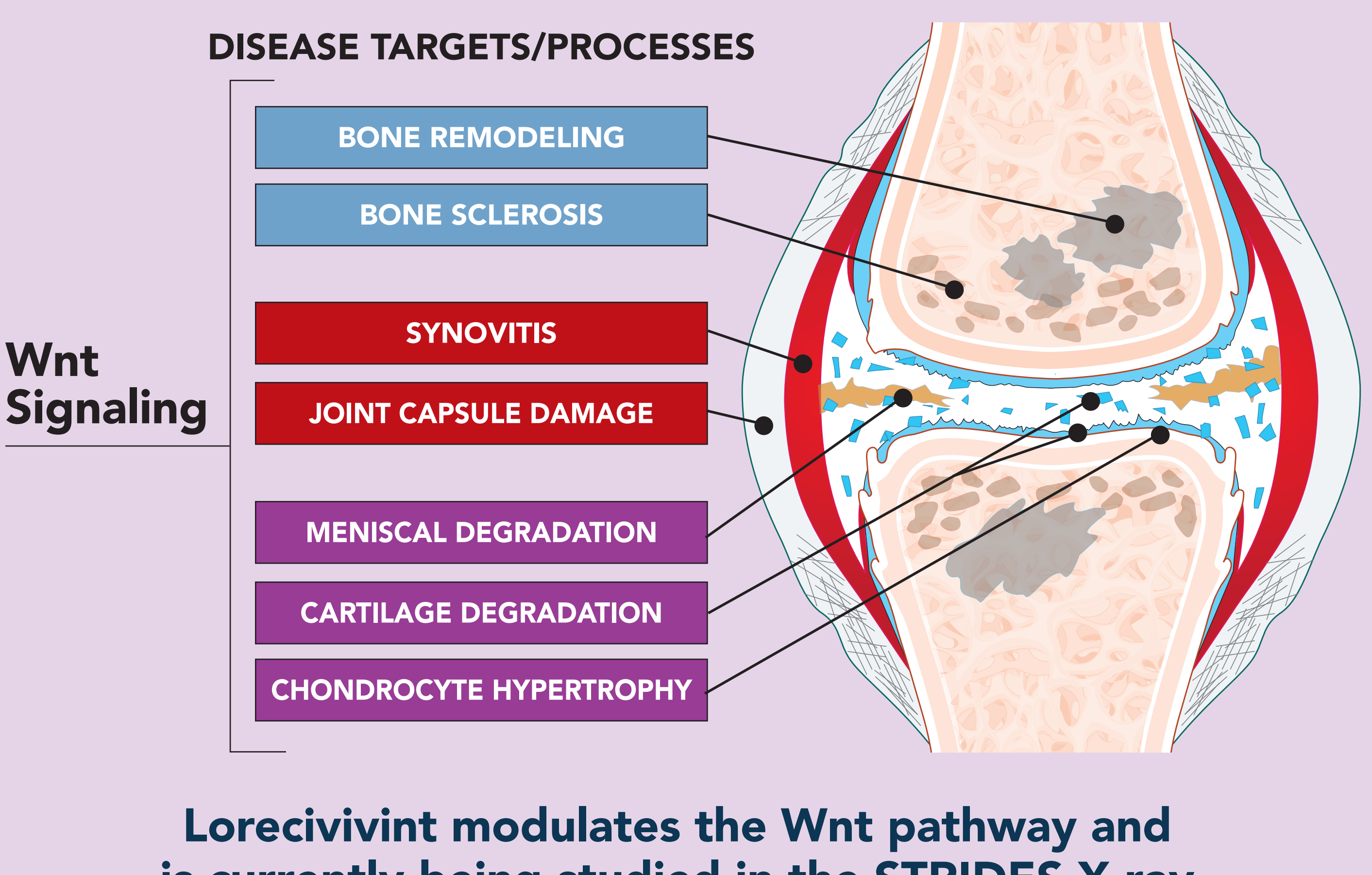
There are therapies that have been shown to inhibit these processes such as nonsteroidal anti-inflammatory drugs and corticosteroids.[2-4]

2

The Wnt Pathway

Wnts are signaling glycoproteins that control cell proliferation, differentiation, apoptosis, migration of cell types, and cell survival.

Wnt signaling molecules and regulators are abnormally activated and/or suppressed in OA. It is hypothesized that agonists and antagonists of Wnts may be potential candidates for OA treatment.



Lorecivivint modulates the Wnt pathway and is currently being studied in the STRIDES-X-ray phase 3 trial (NCT03928184).[6]

3

Nerve Growth Factor

Nerve growth factor (NGF) is a neurotrophin that activates TrkA receptors on nociceptive neurons. NGF is increased in OA and is believed to play a role in the growth of nociceptive nerve fibers. Blocking the binding of NGF to its receptor interrupts/blocks the pain response pathway. Antibodies directed against NGF may be useful in the management of OA.

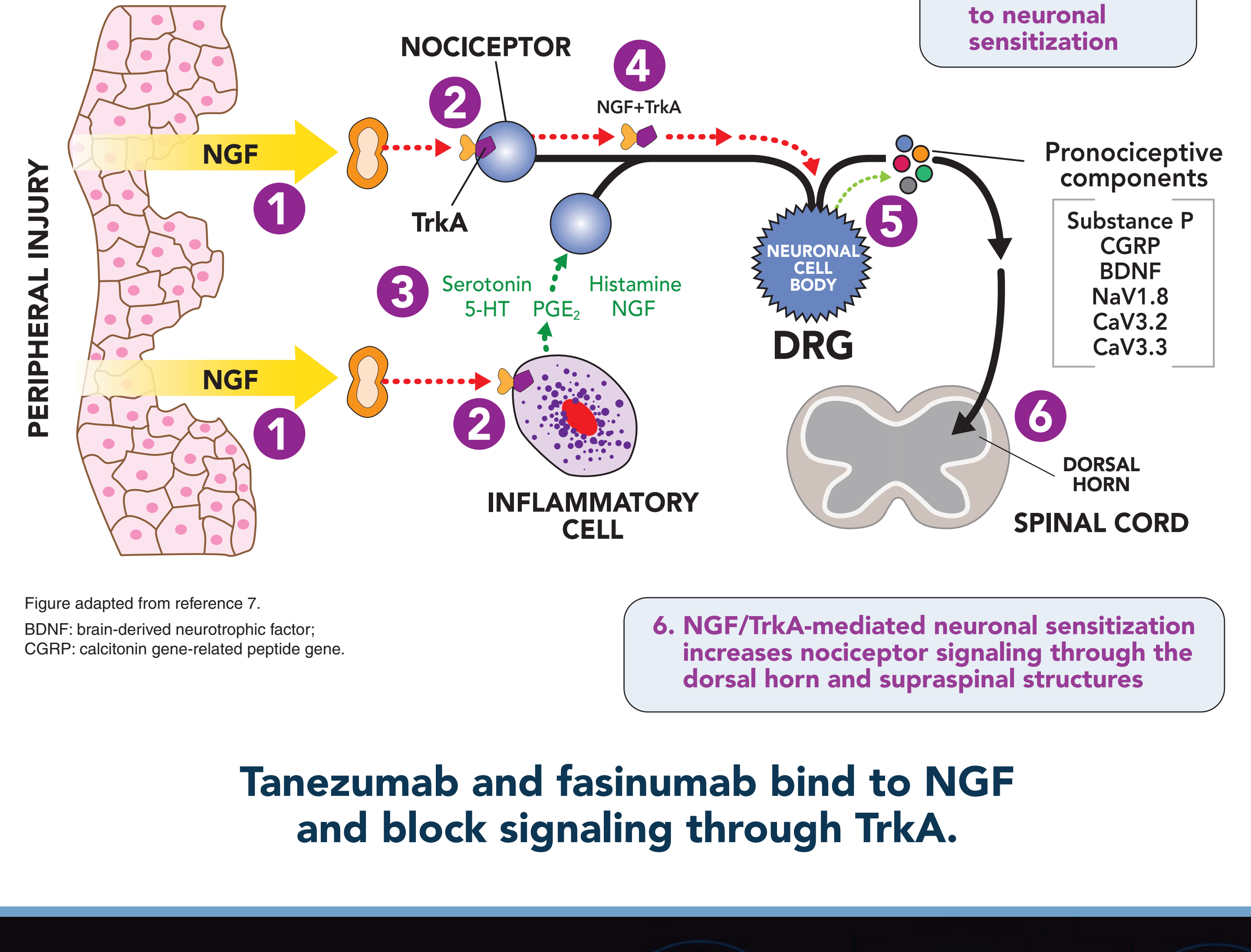


Figure adapted from reference 7.

BDNF: brain-derived neurotrophic factor;
CGRP: calcitonin gene-related peptide gene.

Tanezumab and fasinumab bind to NGF and block signaling through TrkA.

SUMMARY

- Pain associated with OA is a leading cause of loss of mobility/function and disability.
- Traditional treatment options focus on symptom management.
- New and emerging therapies for the management of pain in OA are evolving rapidly. These treatments target the inflammatory process, the Wnt pathways, and the NGF pathway.

REFERENCES

1. Osteoarthritis Research Association International. Osteoarthritis: a serious disease, submitted to the U.S. Food and Drug Administration December 1, 2016. https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf. Accessed August 18, 2020.
2. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. *Nat Rev Drug Discov*. 2014;13(7):533-548.
3. van den Bosch MHJ. Inflammation in osteoarthritis: is it time to dampen the alarm(in) in this debilitating disease? *Clin Exp Immunol*. 2019;195(2):153-166.
4. Sofat N, Kuttapitiya A. Future directions for the management of pain in osteoarthritis. *Int J Clin Rheumtol*. 2014;9(2):197-276.
5. Lories RJ, Monteagudo S. Review Article: Is Wnt Signaling an Attractive Target for the Treatment of Osteoarthritis? *Rheumatol Ther*. 2020;7(2):259-270.
6. Yazici Y, McAlindon TE, Gibofsky A, et al. Lorecivivint, a novel intraarticular CDC–like kinase 2 and dual–specificity tyrosine phosphorylation–regulated kinase 1A inhibitor and Wnt pathway modulator for the treatment of knee osteoarthritis: a phase II randomized trial. *Arthritis Rheumatol*. 2020.doi:10.1002/art.41315
7. Schmelz M, Mantyh P, Malfait AM, et al. Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety. *Pain*. 2019;160(10):2210-2220.

This activity is jointly provided by AKH Inc., Advancing Knowledge in Healthcare and Catalyst Medical Education, LLC.