

Objectives



Review the mechanisms of action and therapeutic effects of mesenchymal cells.



Evaluation of the efficacy and safety of DogStem® and Librela®.



Assessment of the role of NGF in canine osteoarthritis.

Role of the nerve growth factor (NGF)

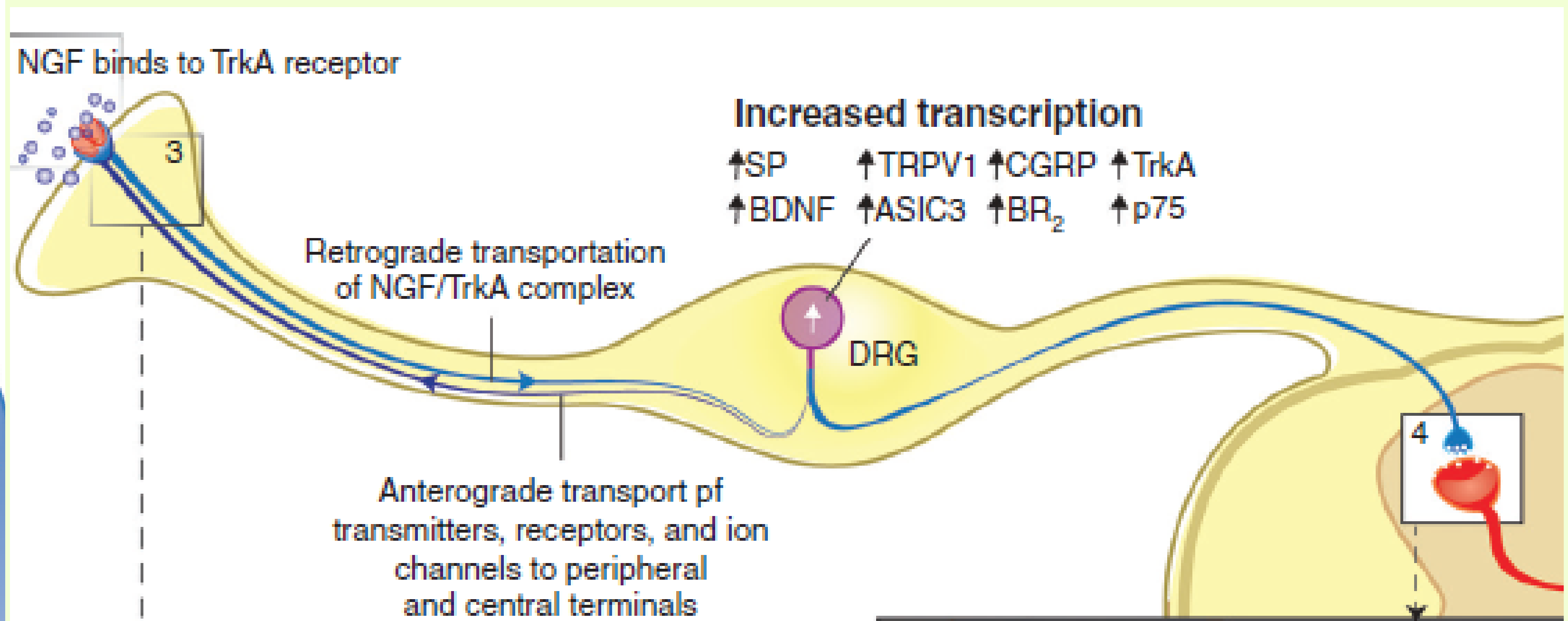
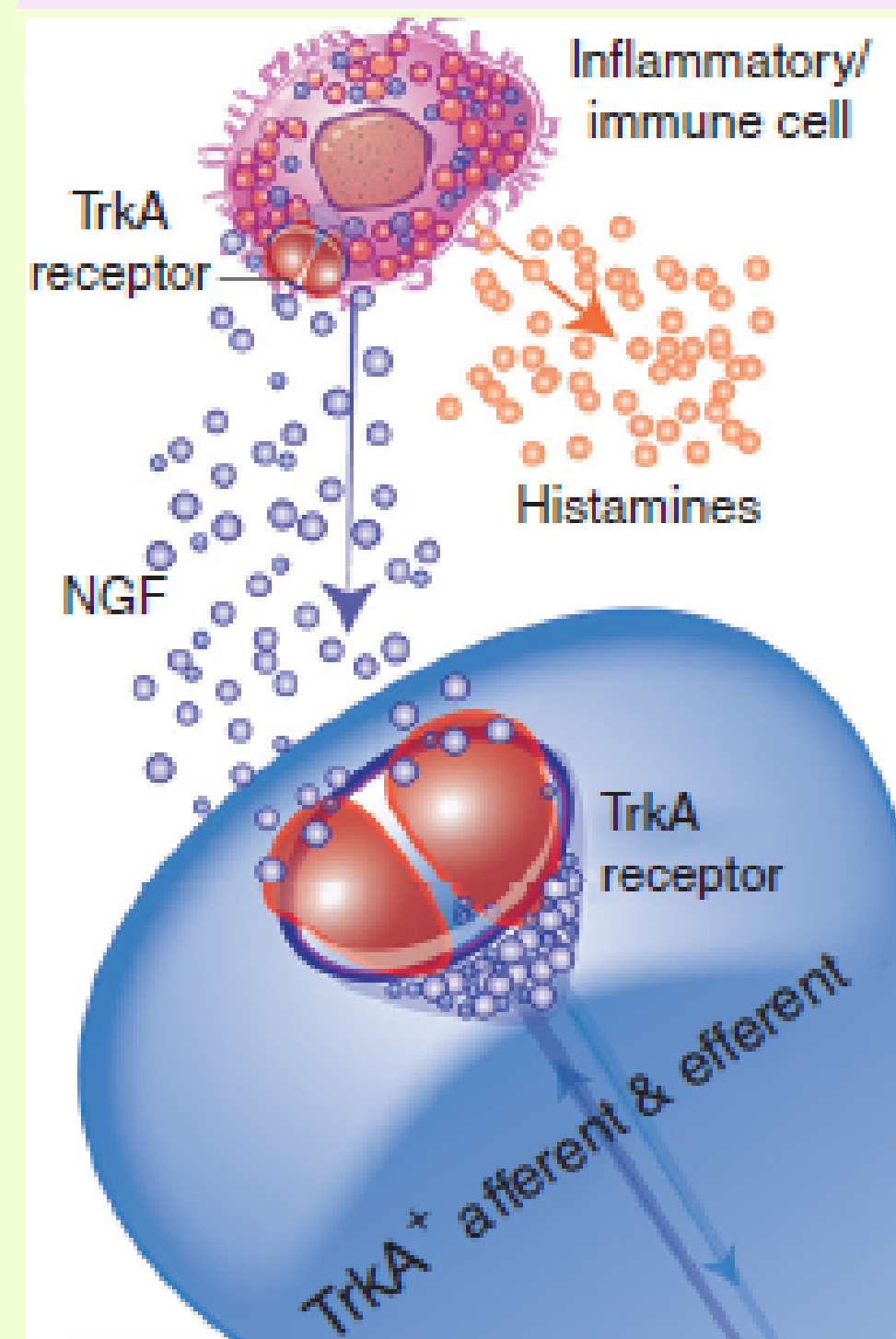


Figure 1. The role of the NGF in canine osteoarthritis (Enomoto et al. 2019).

DogStem®

IMMUNO-
MODULATION

- First and unique drug with mesenchymal stem cells registered in European Union.
- 7.5×10^6 MSCs of the equine umbilical cord, administered intraarticular in the knee or elbow.
- No relevant clinically adverse effects.
- 62,86% improve $\geq 5\%$ in platform force at 8-week post-treatment.

ANTI-
INFLAMMATORY

Pharmacodynamics

- MSCs are stimulated by proinflammatory mediators of the OA joint, such as prostaglandin E2 (PGE2). It decreases the proliferation of CD4+ (helper) and CD8+ T (cytotoxic) lymphocytes, and at the same time, increases the concentration of Treg, helping to reduce the response of the adaptive immune system against MSCs. It induces an anti-inflammatory phenotype of dendritic cells (DCs) and T helper cells 1 and 2 (Th-1 and Th-2), decreasing TNF- α secretion by DCs type I and increasing IL-10 secretion by DCs type II and IL-4 by Th-2.
- Modulation of macrophage activity promoting the synthesis of M2 macrophages (anti-inflammatory phenotype).
- Reduction of matrix metalloprotease expression, blocking extracellular matrix degradation and pro-catabolic state.

ANTI-FIBROSIS

REDUCED
APOPTOSIS

CARTILAGE
REPAIR

Librela®

Pharmacodynamics

- Canine immunoglobulin G2 (IgG2) monoclonal antibody.
- It binds to canine NGF, blocking the complex trkA-FCN/p75-NGF.
- Peripheral and central sensitization of nociceptive neurons blocking.
- Pain signals and releasing of proinflammatory mediators (including NGF) are reduced.

Pharmacokinetics

Cmax: $6.10 \pm 1.68 \mu\text{g/ml}$; Tmax 5.6 days; Bioavailability of $83.5 \pm 15.8\%$. The soluble form enters cells by endocytosis or transcytosis through the vascular epithelium into tissue compartments, mediated by the neonatal Fc receptor (FcRn), expressed on the membrane of immune cells. Endosomes capture the antibody, producing the IgG-FcRn complex, and transport it to the cell surface, to release it into the bloodstream. It isn't excreted by the kidney but by lysosomal degradation, and isn't metabolized in the liver either.

Efficacy

With a monthly subcutaneous injection at 0.5-1.0 mg/, a statistically significant improvement is observed from the 1st week on the pain severity score for three months through the "Canine Brief Pain Inventory" or CBPI, and an extension of the therapeutic effect up to 9 months. A maximum effect is achieved at the second dose ($\pm 52.6\%$ of dogs; $p=0.0001$). It does not generate clinically significant adverse effects and has a low incidence of mild immunogenicity, without reducing efficacy and associated adverse effects.

Conclusions

The two drugs effectively reduce the clinical signs associated with canine OA, improving the dog's life quality and mobility. DogStem® has a powerful immunomodulatory and anti-inflammatory effect, and Librela® blocks the NGF pain signal. They are alternatives in dogs that do not respond to conventional treatments and/or have kidney, liver failure, or other contraindications.

Time point	Gait analysis			
	Variable	EUC-MSCs	Placebo	P value
4 wk	n	27	34	0.1605
	Efficacy	40,74%	20,6%	
8 wk	n	35	37	<0.0001
	Efficacy	62,86%	8,00%	
12 wk	n	29	37	0.0054
	Efficacy	48,27%	10,81%	

Figure 2. Gait analysis by force platform at weeks 4, 8 and 12. Extracted from Punzón et al. (2022).