28th Annual Gabor Racz Advanced Interventional Pain Conference and Workshop
Budapest, Hungary August 25-27, 2025

Neuroinflammation and Pain: Cytokine Modulation at the DRG as a Therapeutic Frontier

Diego Benítez Pareja, MD, FIPP, CIPS

Conflicts of Interest

The role of neuroinflammation in the transition of acute to chronic pain and the opioid-induced hyperalgesia and tolerance

Marco Echeverria-Villalobos[1]*, Victor Tortorici[2,3], Beatriz E. Brito[4], David Ryskamp[5], Alberto Uribe[1] and Tristan Weaver[1]

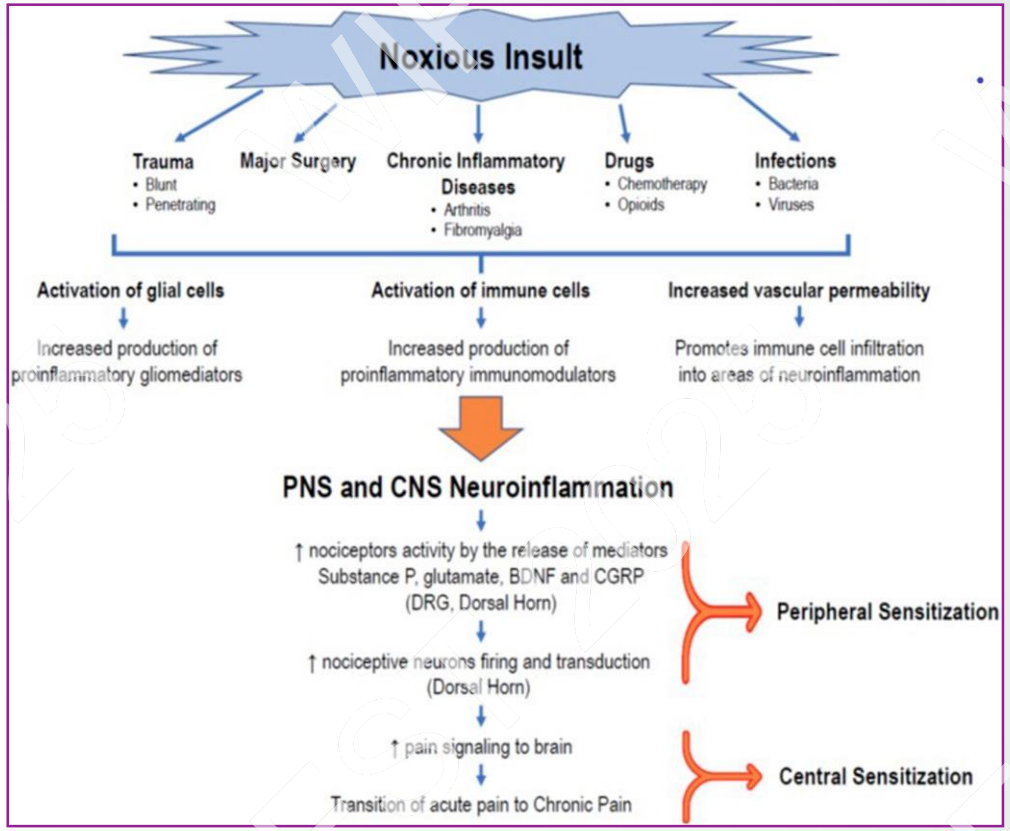
Neuroinflammation

Activation of Glial and Immune cells

Proinflamatory mediators

Neuroinflamatory state

Transition to neuropathic and chronic pain

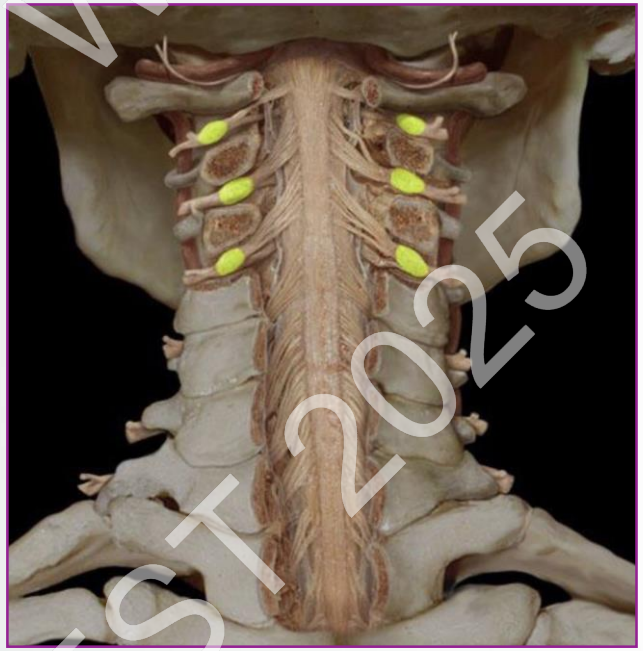


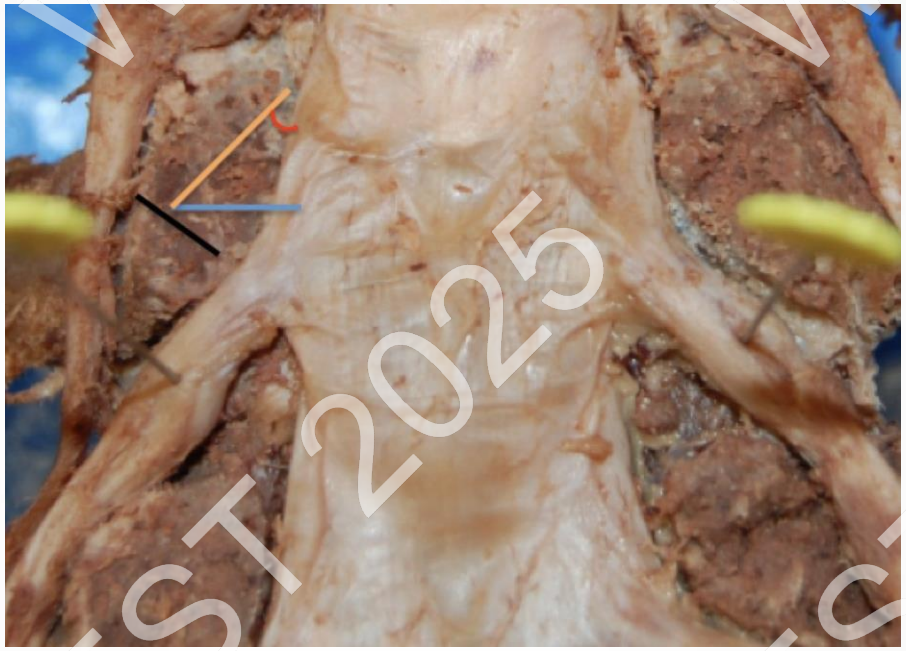
Pain. 2023 Feb 1;164(2):362-374. doi: 10.1097/j.pain.0000000000002708. Epub 2022 Jun 7.

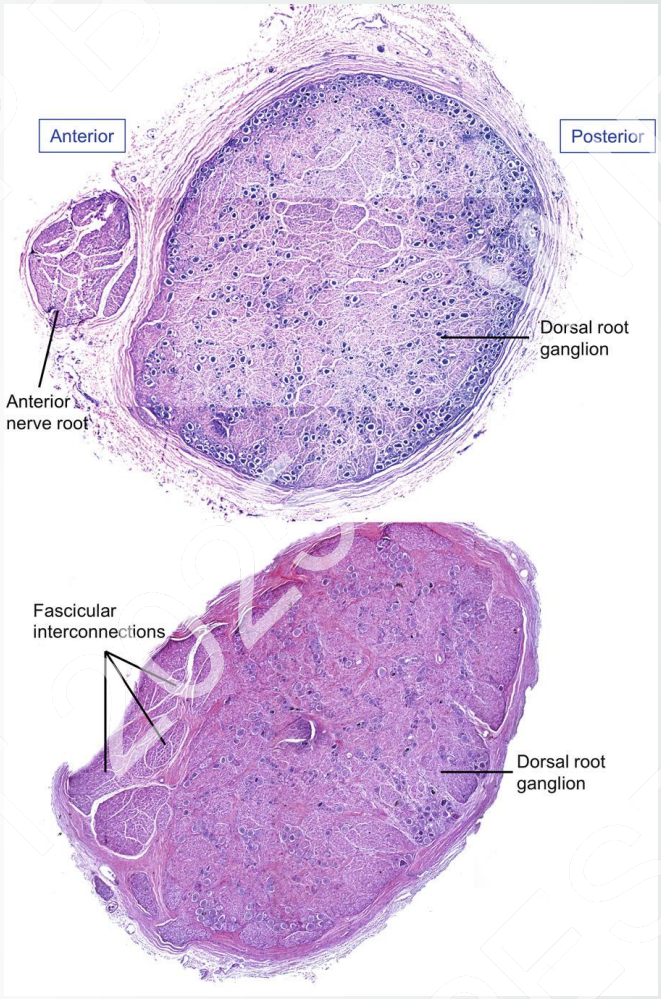
Microglia and macrophages contribute to the development and maintenance of sciatica in lumbar disc herniation

Xuan Lu [1], Lunhao Chen [1], Chao Jiang [1], Kelei Cao [2 3 4], Zhihua Gao [2 3 4], Yue Wang [1]

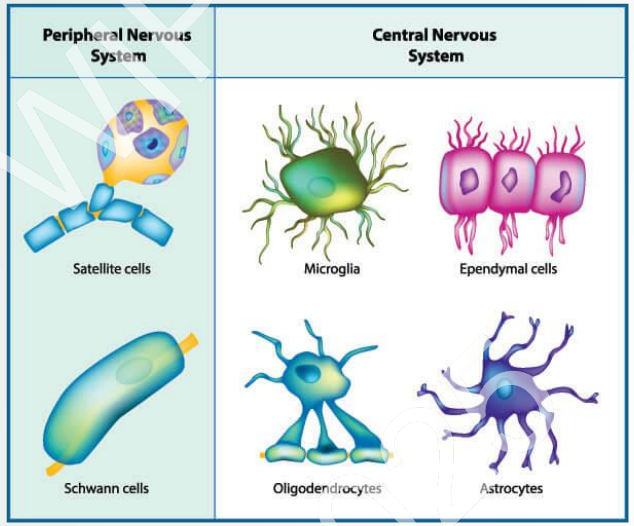
Neuroinflammation

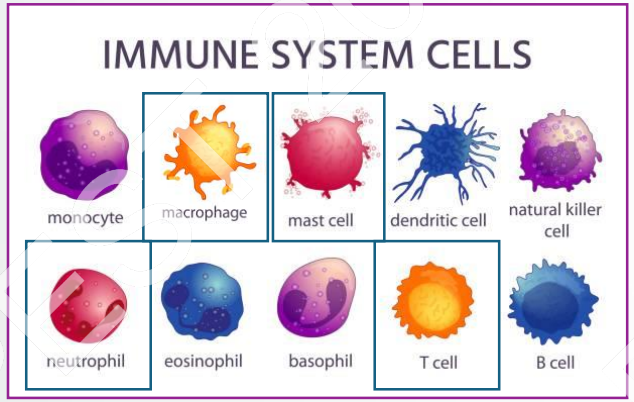


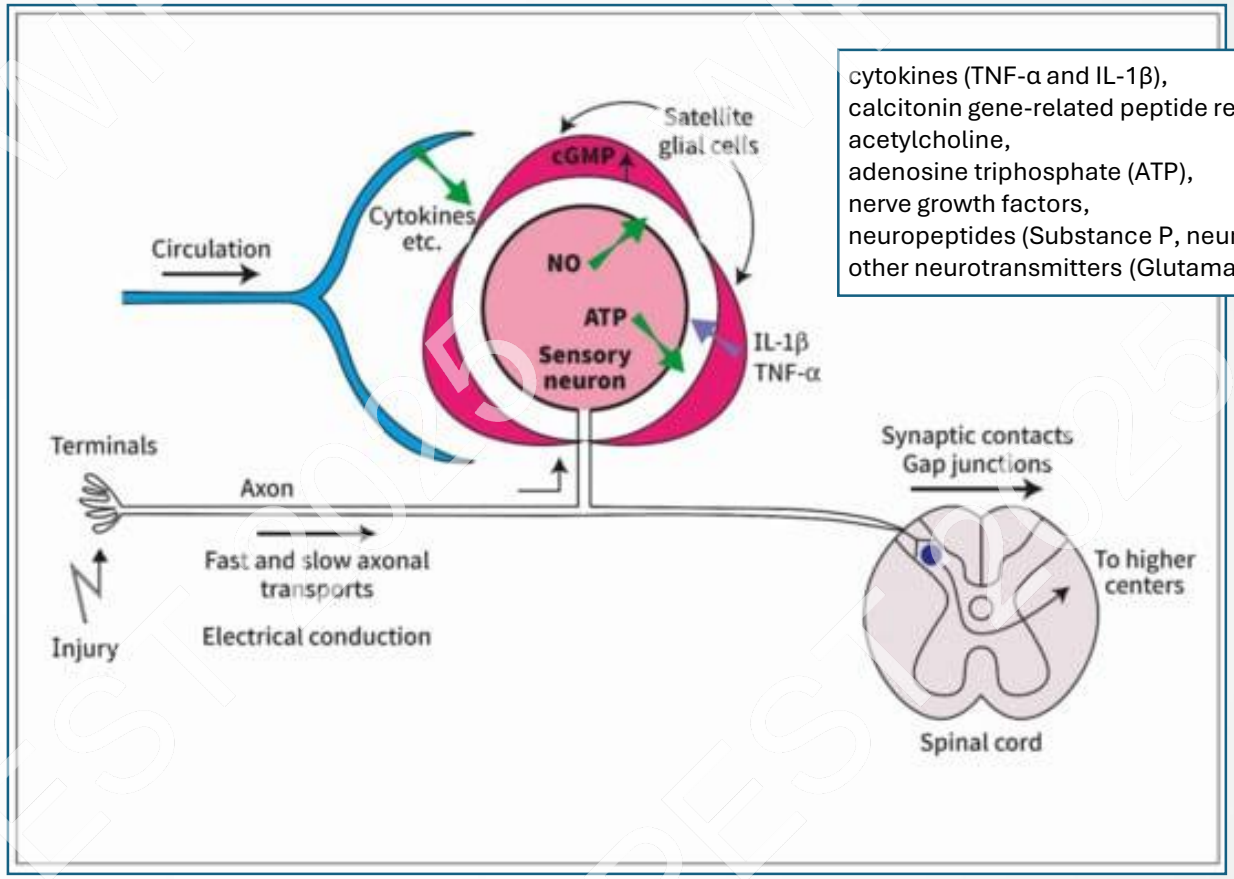




Neuroinflammation



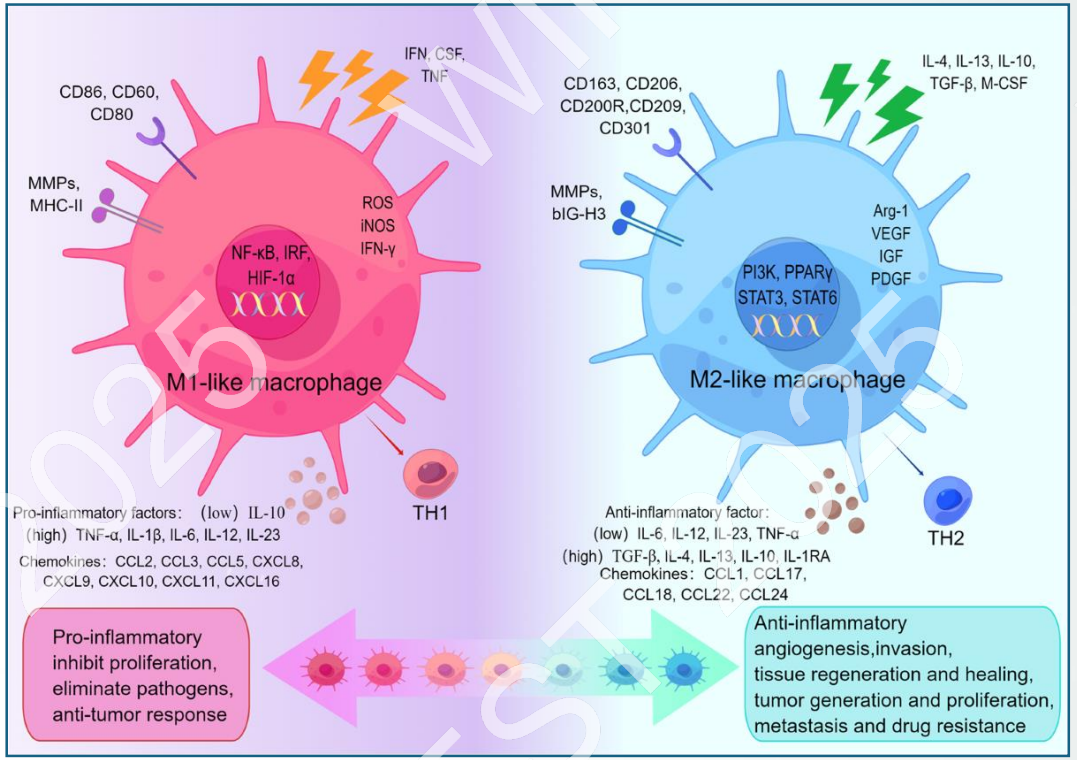




cytokines (TNF-α and IL-1β),
calcitonin gene-related peptide receptor (CGRP),
acetylcholine,
adenosine triphosphate (ATP),
nerve growth factors,
neuropeptides (Substance P, neurokinin)
other neurotransmitters (Glutamate, GABA, serotonin, etc)

DRG Macrophages
It all depends on the context

"exhibit phenotypic plasticity and can adopt different activation states in response to different conditions"

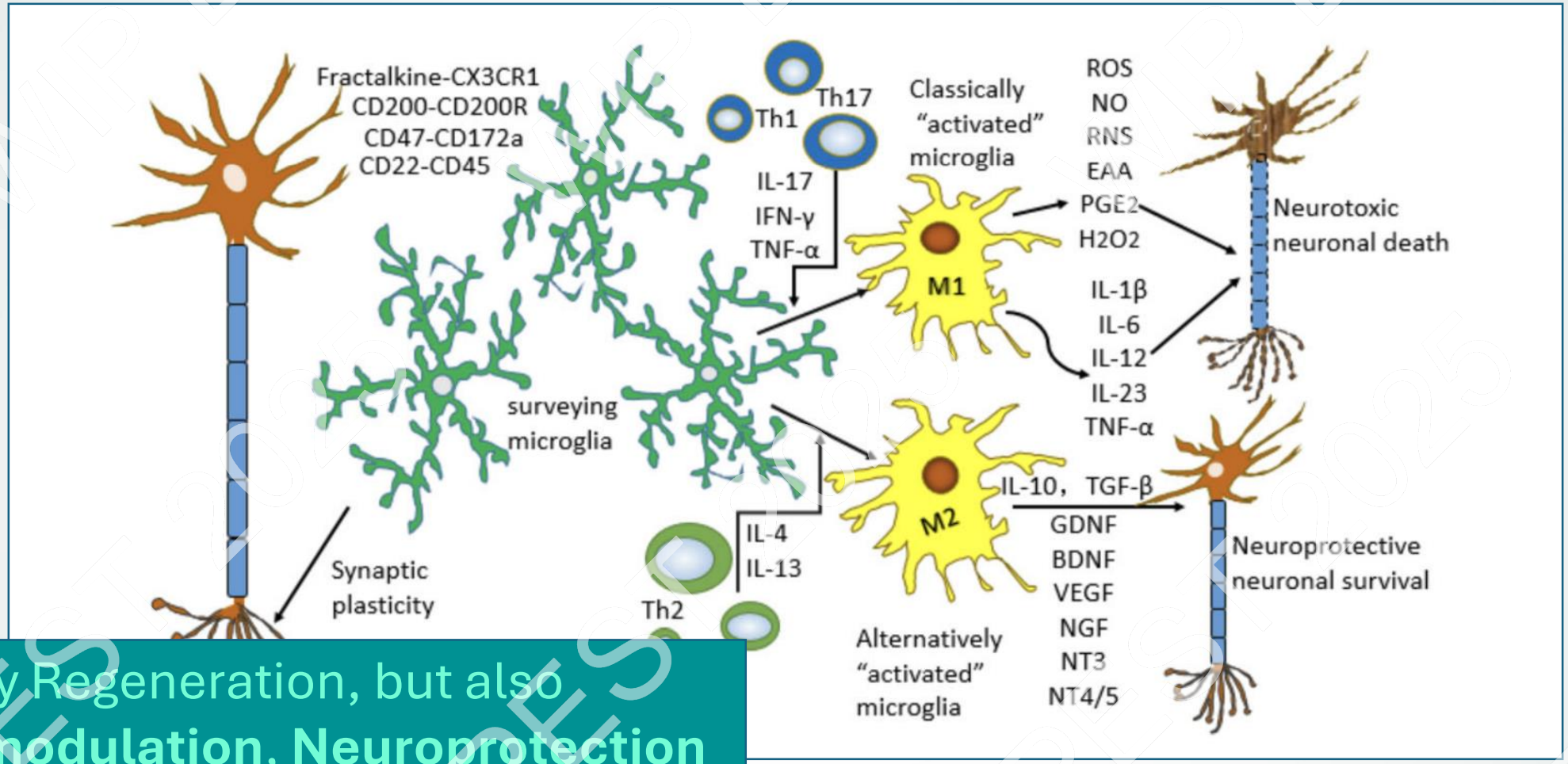


Paolicelli RC, et al. Microglia states and nomenclature: A field at its crossroads. Neuron. 2022 Nov 2;110(21):3458-3483. doi: 10.1016/j.neuron.2022.10.020. PMID: 36327895; PMCID: PMC9999291.

Mol Neurobiol
DOI 10.1007/s12035-016-0245-0

Role of Microglia in Neurological Disorders and Their Potentials as a Therapeutic Target

Li Du[1] · Ying Zhang[1] · Yang Chen[1] · Jie Zhu[1,2] · Yi Yang[1] · Hong-Liang Zhang[1,3]



Not only Regeneration, but also
Neuromodulation, Neuroprotection

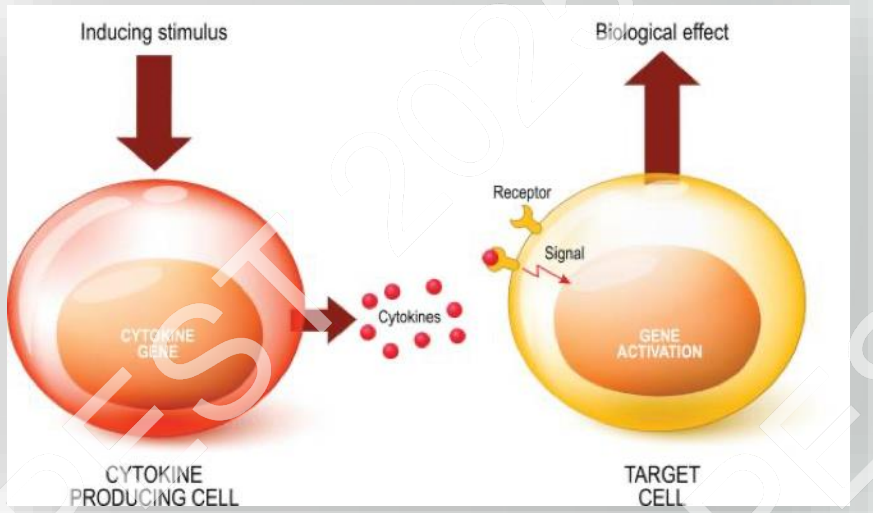
What are Citokines?

CYTOKINES ARE **THE LANGUAGE** WITH WHICH CELLS INTERACT

They are low molecular weight proteins (glycoproteins)

Produced by multiple cell types, including immune and no immune cells

Chemical messengers, regulating:
Immune response
Inflammation
Cell proliferation
Differentiation
Gene expression
Others…



How do they work?

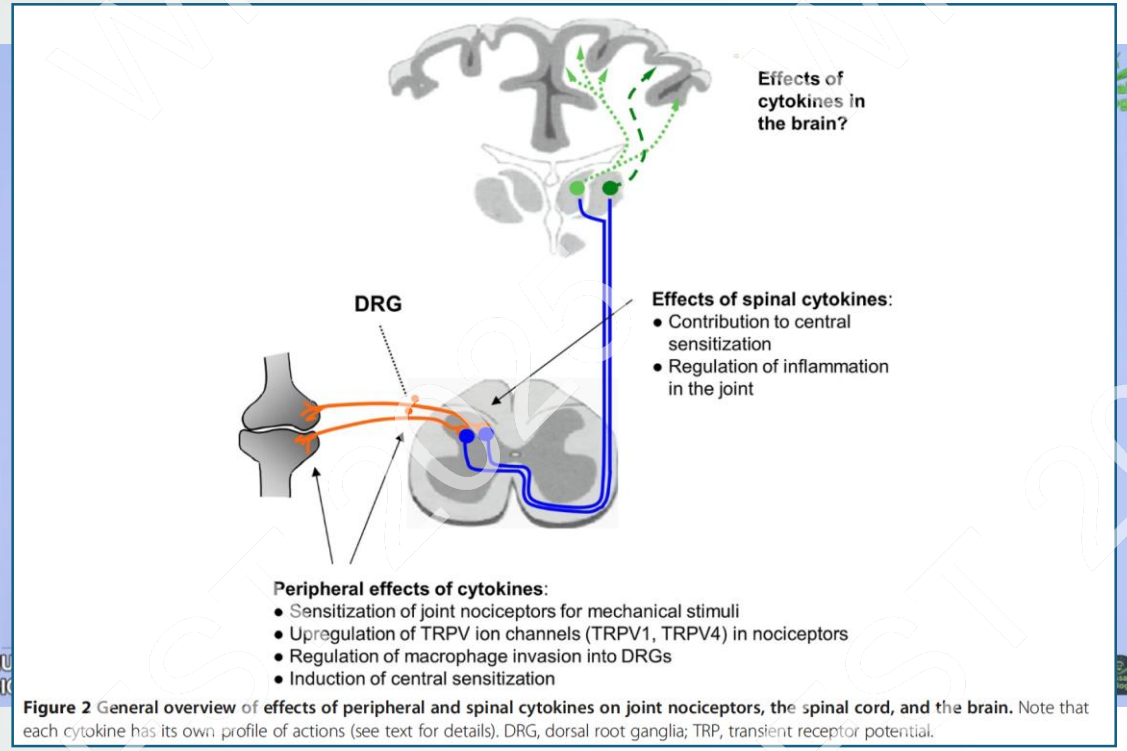
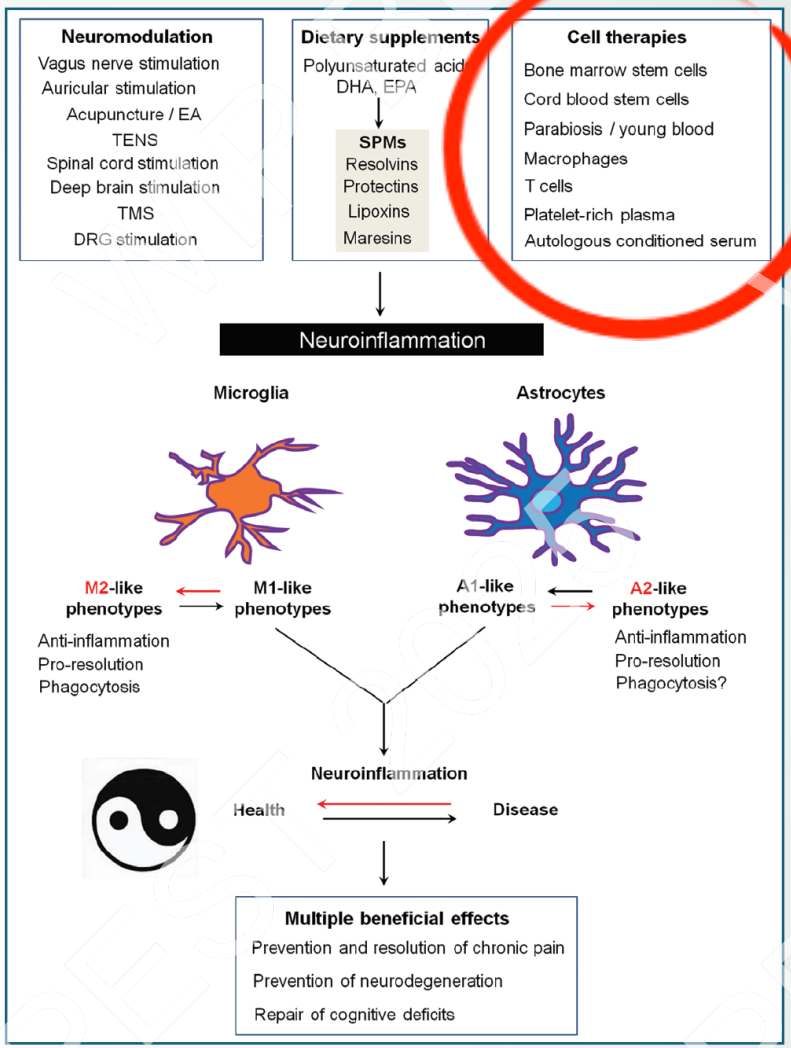


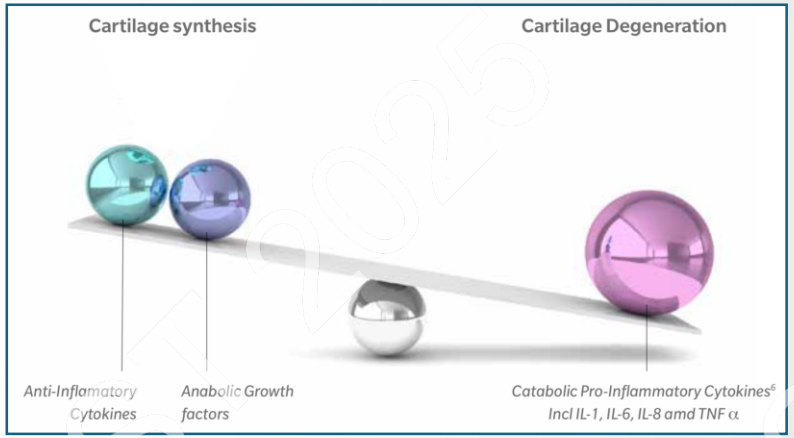
Figure 2 General overview of **effects of peripheral and spinal cytokines on joint nociceptors, the spinal cord, and the brain.** Note that each cytokine has its own profile of actions (see text for details). DRG, dorsal root ganglia; TRP, transient receptor potential.



How do they work?

Pro-inflammatory Th1-type, stimulatory	Anti-inflammatory Th2-type, inhibitory	Multifunctional
IFNγ	IL-4, IL-10, IL-1ra, IL-2	IL3, IL-1β
TNFα	TNFsr	MCP-1
IP-10	TGF-β2	sCD40L
IL-2, IL-6, IL-8,		Growth factors:
IL-12, IL-17		IL3 and G-CSF

Abbreviations: G-CSF, granulocyte colony stimulating factor; IFNγ, interferon-gamma; IL, interleukin; IP-10, inducible protein-10; MCP-1, monocyte chemoattractant protein-1; sCD40L, soluble CD40 ligand; TGF-β2, tumor growth factor β2; TNFα, tumor necrosis factor α; TNFsr, tumor necrosis factor soluble receptor.



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Neuroinflammation and Pain: Cytokine Modulation at the DRG as a Therapeutic Frontier

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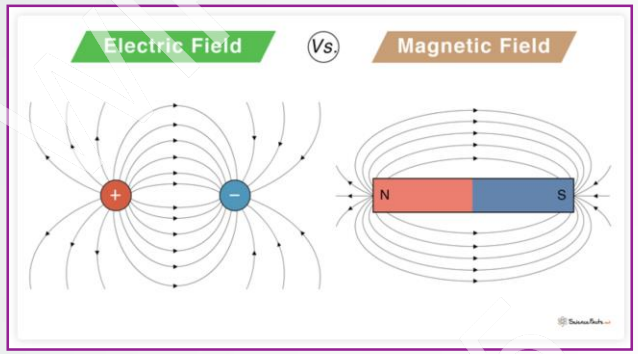
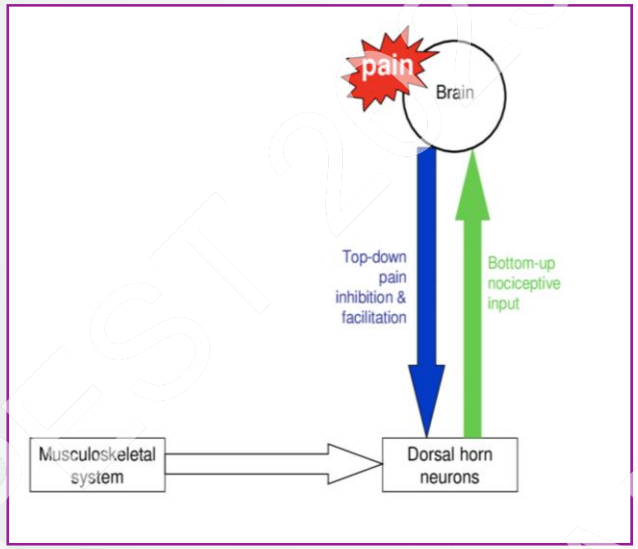
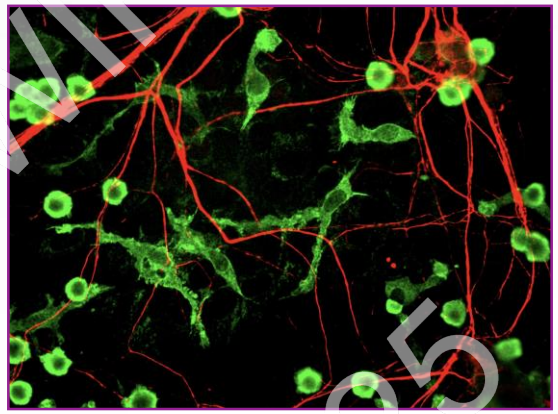
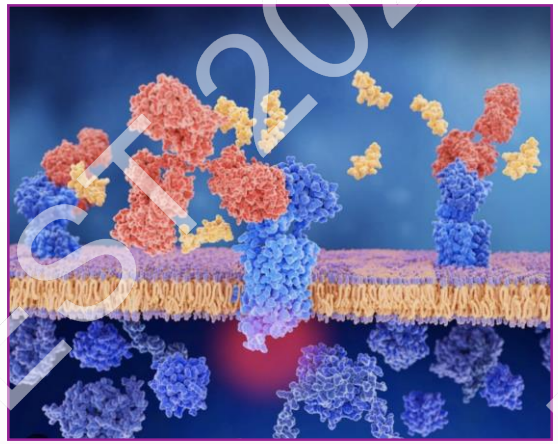
Non-Ablative Mechanisms of Radiofrequency

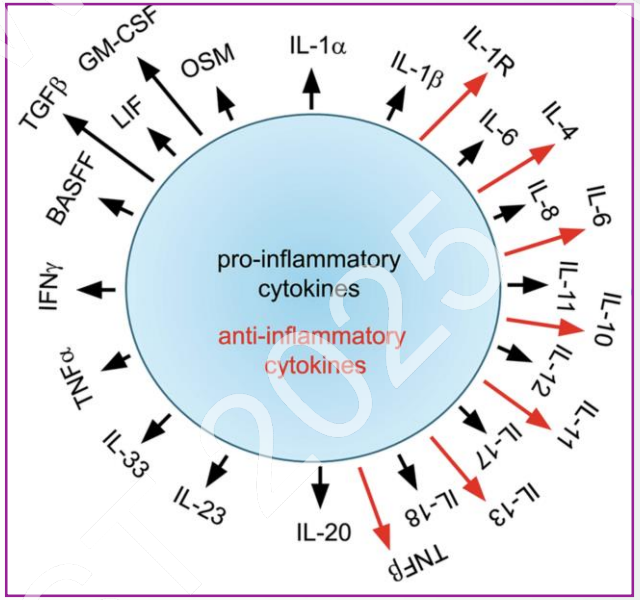
No tissue damage











Sluijter ME, Cosman ER, Rittman WB, van Kleef M. The effects of pulsed radiofrequency field applied to the dorsal root ganglion: a preliminary report. Pain Clin. 1998;11:109–17.

Non-Ablative Mechanisms of Radiofrequency

No tissue damage

Table 2.1 Non-ablative mechanism of RF

Types of mechanism	Mechanism of action of RF
1. Electromagnetic fields	Neuromodulatory effect
2. Modulate pain signal transmission	Reduces the conduction of pain signals through the nerve fibers
3. Microglia activation	Morphological change + change in releasing various cytokines and chemokines involved in pain signaling
4. Gene expression	Alternation of gene expression involved in pain
5. C-Fos (an immediate-early gene used as an indirect marker of neuronal activity)	Alters C fiber transmission associated with greater c-Fos expression in the dorsal horn
6. MET-encephalin (an endogenous opioids)	Increases the amount of M-ENK in the spinal cord to regulate nociceptive pain
7. TNF-α, IL-6, IL-1	Alter immune cells Reduce the expression of proinflammatory cytokines Relieve neuropathic pain by attenuating neuroinflammation
8. Calcitonin gene-related peptide (a neuropeptide)	Breaks the pain cycle by inhibiting CGRP expression, changes in the nociception transduction pathway
9. Activating translation factor 3 (a marker of cellular stress, increases in neurons and glial cells after axotomy)	Extension of PRF exposure times did not increase the antiallodynic effect but could also have neurolytic effects
10. Neurotransmitter: BDNF, PI3K, and p-ERK (released in the spinal cord in a microglia-dependent manner, developing chronic pain and pain sensitization)	PRF to DRG can reduce neuropathic pain by suppressing microglia and downregulated levels of them
11. Excitatory amino acids released in the spinal cord (in a microglia-dependent manner, developing chronic pain and pain sensitization)	Reduce inflammatory pain with spinal dorsal horn modulation; suppress EAAs-citrulline release and alter glutamate receptor
12. Regenerative mechanism	The electrical stimulation can increase chondrocyte proliferation and matrix synthesis; increase DNA synthesis and increase GAG proliferation and synthesis in human cartilage
13. IGF-2 (a protein involved in prenatal growth and development)	This effect of immediate PRF is achieved through the downregulation of IGF 2
14. Cellular and histological changes in RA	PRF: Changes in mitochondrial membranes and appearance, disorganized microfilaments and microtubules CRF: Changes such as mitochondrial degeneration and loss of nuclear membrane integrity

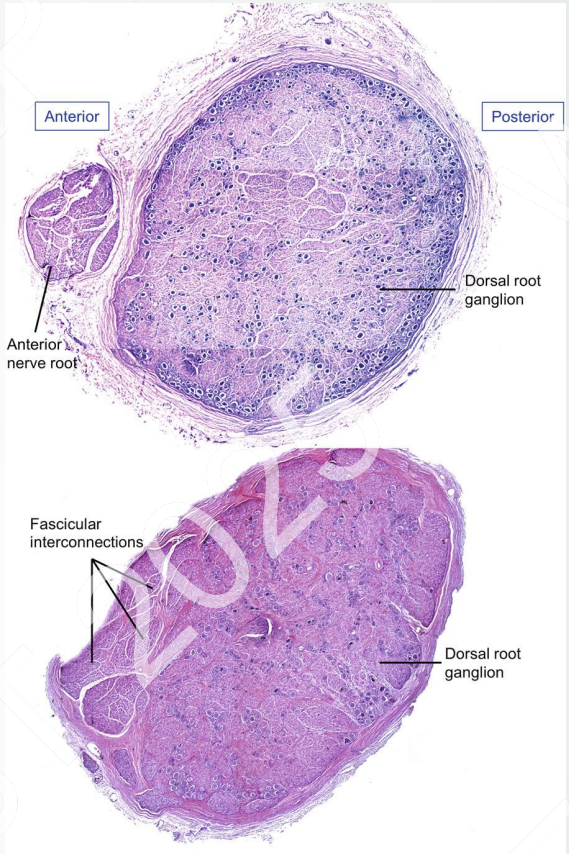
Sluijter ME, Cosman ER, Rittman WB, van Kleef M. The effects of pulsed radiofrequency field applied to the dorsal root ganglion: a preliminary report. Pain Clin. 1998;11:109–17.

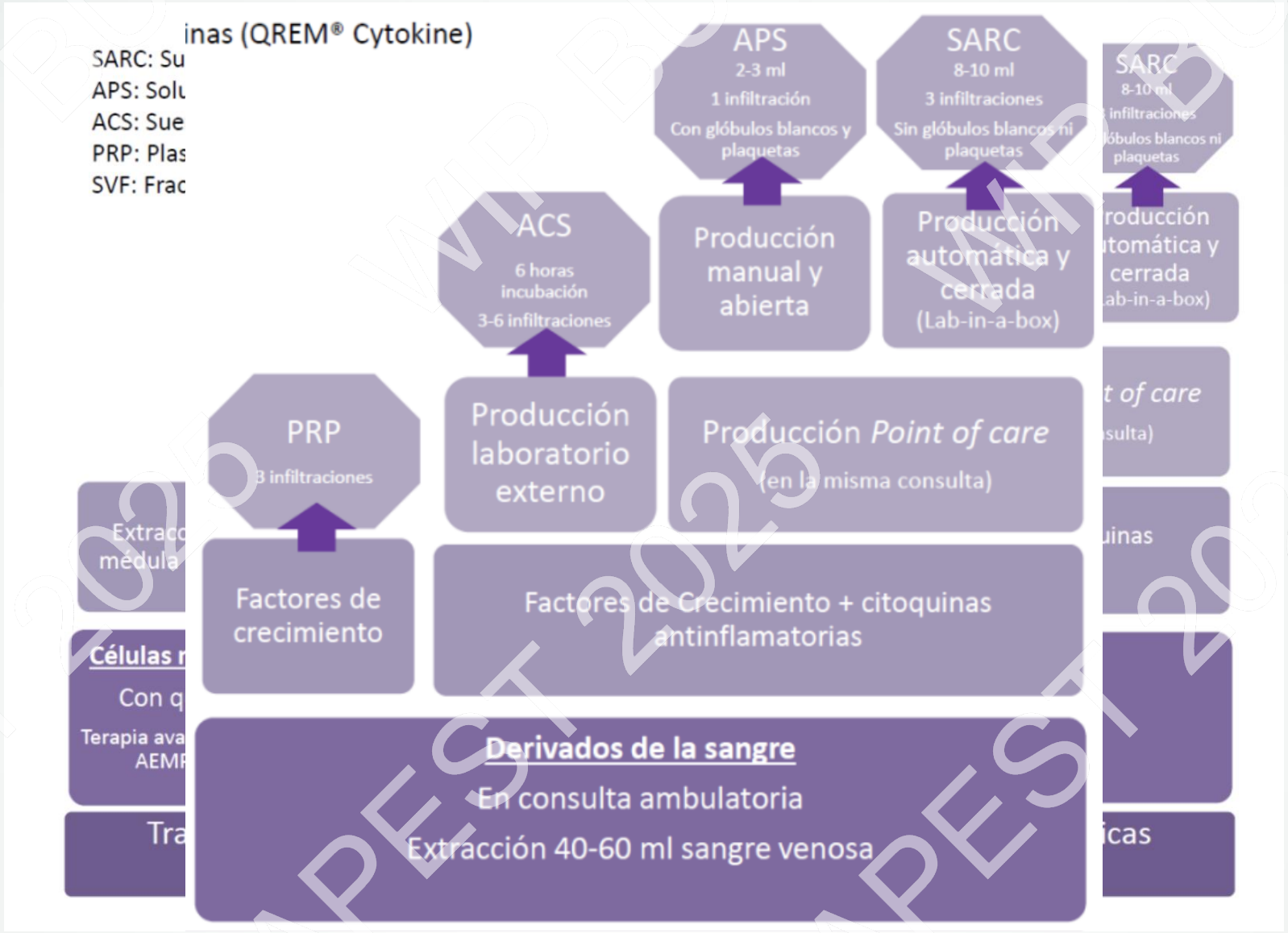
Change the paradigm

ELECTROMAGNETICALLY → PRF

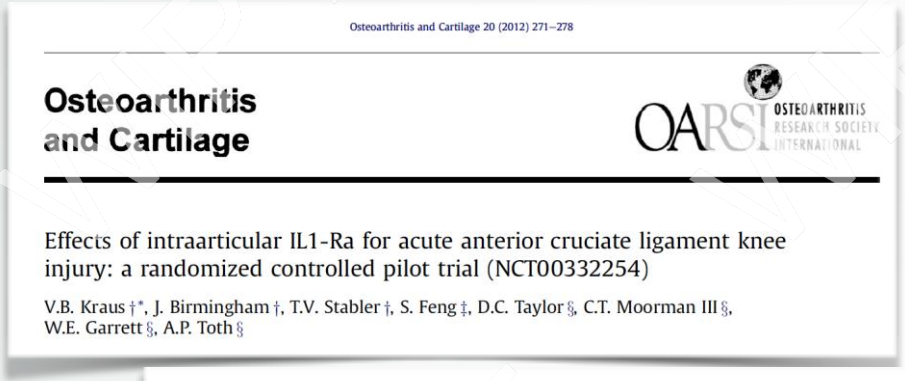
NEUROCHEMICALLY → CYTOKINES

DRG




inas (QREM® Cytokine)
SARC: Su
APS: Solu
ACS: Sue
PRP: Plas
SVF: Frac
APS
2-3 ml
1 infiltración
Con glóbulos blancos y plaquetas
SARC
8-10 ml
3 infiltraciones
Sin glóbulos blancos ni plaquetas
SARC
8-10 ml
infiltraciones
lóbulos blancos ni plaquetas
ACS
6 horas incubación
3-6 infiltraciones
Producción manual y abierta
Producción automática y cerrada (Lab-in-a-box)
roducción
tomática y
cerrada
ab-in-a-box)
PRP
3 infiltraciones
Producción laboratorio externo
Producción Point of care
(en la misma consulta)
t of care
sulta)
Extracc
médula
uinas
Factores de crecimiento
Factores de Crecimiento + citoquinas antinflamatorias
Células
Con q
Terapia ava
AEMP
Tra
Derivados de la sangre
En consulta ambulatoria
Extracción 40-60 ml sangre venosa
icas

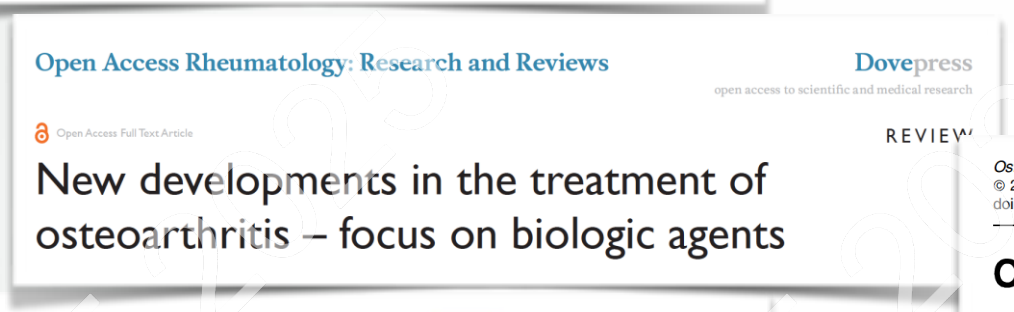
AUTOLOGOUS CONDITIONED SERUM


Osteoarthritis and Cartilage 20 (2012) 271–278

Osteoarthritis and Cartilage

Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254)

V.B. Kraus †*, J. Birmingham †, T.V. Stabler †, S. Feng ‡, D.C. Taylor §, C.T. Moorman III §, W.E. Garrett §, A.P. Toth §


Open Access Rheumatology: Research and Reviews

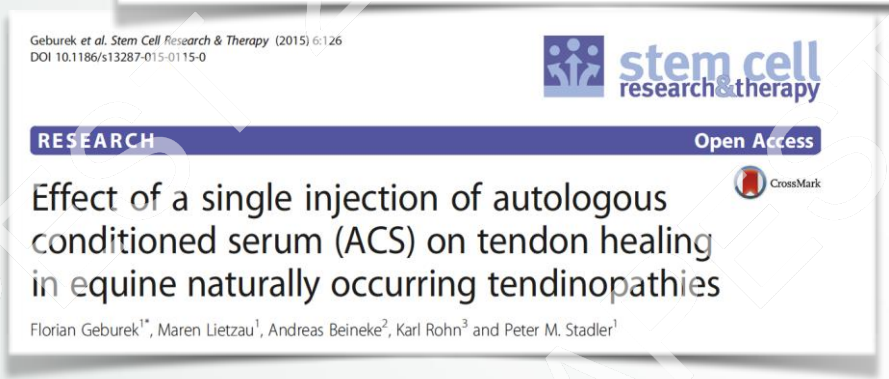
Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

New developments in the treatment of osteoarthritis – focus on biologic agents

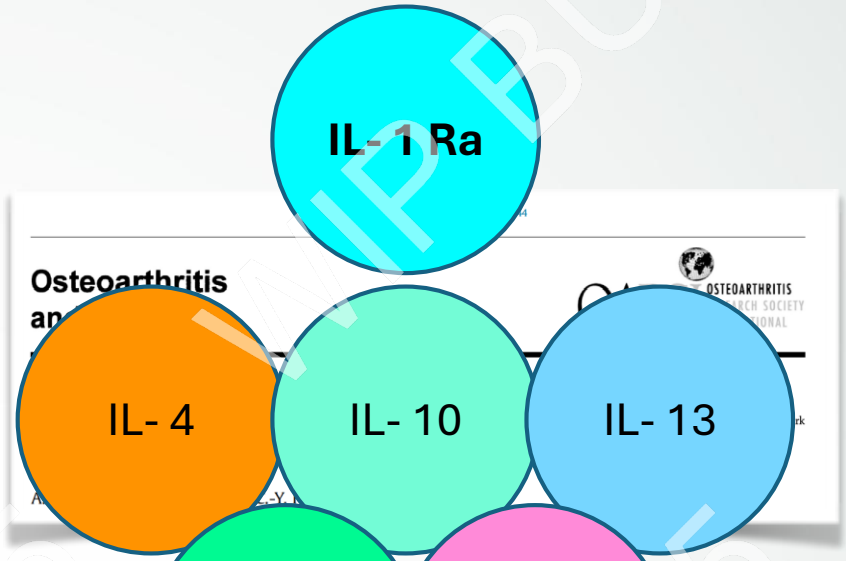

Geburek et al. Stem Cell Research & Therapy (2015) 6:126
DOI 10.1186/s13287-015-0115-0

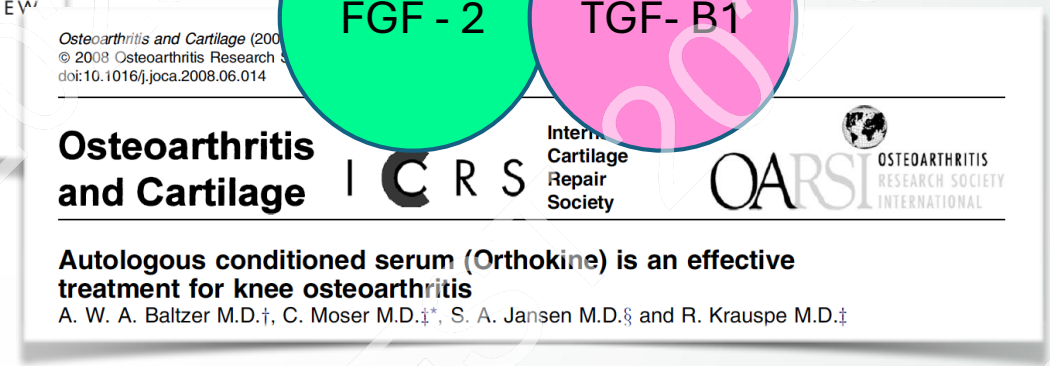
stem cell research&therapy

RESEARCH Open Access

Effect of a single injection of autologous conditioned serum (ACS) on tendon healing in equine naturally occurring tendinopathies

Florian Geburek[1*], Maren Lietzau[1], Andreas Beineke[2], Karl Rohn[3] and Peter M. Stadler[1]




Osteoarthritis and Cartilage (200
© 2008 Osteoarthritis Research
doi:10.1016/j.joca.2008.06.014

Osteoarthritis and Cartilage

ICRS International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis

A. W. A. Baltzer M.D.†, C. Moser M.D.‡*, S. A. Jansen M.D.§ and R. Krauspe M.D.‡

ANTI-INFLAMATORY, REGENERATIVE, CONDROPROTECTIVE

ACS (ORTHOKINE) vs TRIAMCINOLONE

LUMBAR RADICULAR PAIN

EPIDURAL PERINEURAL INJECTION
- 32 patients ACS
- 27 patients TRIAMCINOLONE 5mg
- 25 patients TRIAMCINOLONE 10mg

ONCE PER WEEK, 3 WEEKS

FOLLOW-UP 6 MONTHS

SPINE Volume 32, Number 17, pp 1803–1808

Efficacy of Epidural Perineural Injections With Autologous Conditioned Serum for Lumbar Radicular Compression

An Investigator-Initiated, Prospective, Double-Blind, Reference-Controlled Study

Cordelia Becker, MD,* Stefan Heidersdorf, MD,† Sascha Drewlo, MSc,‡
Sonja Zirke de Rodriguez,† Juergen Krämer, MD,† and Roland Ernst Willburger, MD§

2007

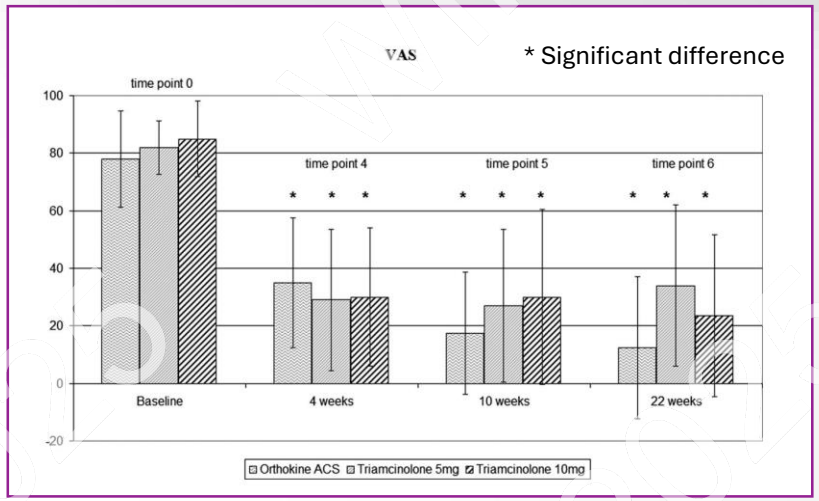


Table 3. Secondary Study Endpoint

Therapy	Time Point 1: Baseline	Time Point 4: 6 Weeks	Time Point 5: 10 Weeks	Time Point 6: 22 Weeks
ACS [mean (SD)]	22.0 (8.3)	13.8 (9.8)	11.2 (10.2)	11.7 (9.2)
Median	23.5	13.0	8.0	10.0
5 mg triamcinolone [mean (SD)]	20.6 (8.1)	12.1 (9.0)	12.4 (9.0)	11.1 (7.1)
Median	19.0	9.0	10.0	10.0
10 mg triamcinolone [mean (SD)]	19.4 (9.9)	11.0 (9.5)	11.0 (10.2)	11.4 (10.3)
Median	19.0	10.0	9.0	9.5

The Oswestry Disability Index (ODI) results in the three treatment groups. Mean (SD) values are given. There was no significant difference between the groups at any time.

ASIAN SPINE JOURNAL
Clinical Study
Asian Spine J 2015;9(6):916-922 • http://dx.doi.org/10.4184/asj.2015.9.6.916

Autologous Conditioned Serum as a Novel Alternative Option in the Treatment of Unilateral Lumbar Radiculopathy: A Prospective Study

Ravi Kumar H. S.[1], Vijay G. Goni[2], Batra Y. K.[3]
[1]Department of Orthopaedics, Mandya Institute of Medical Sciences, Mandya, India

2015

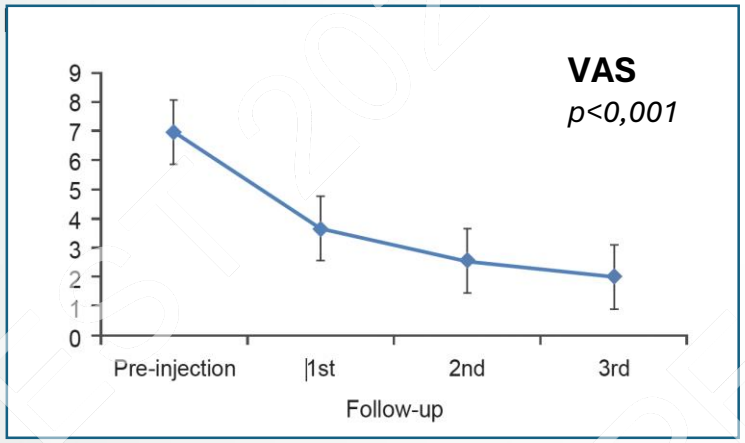
20 patients

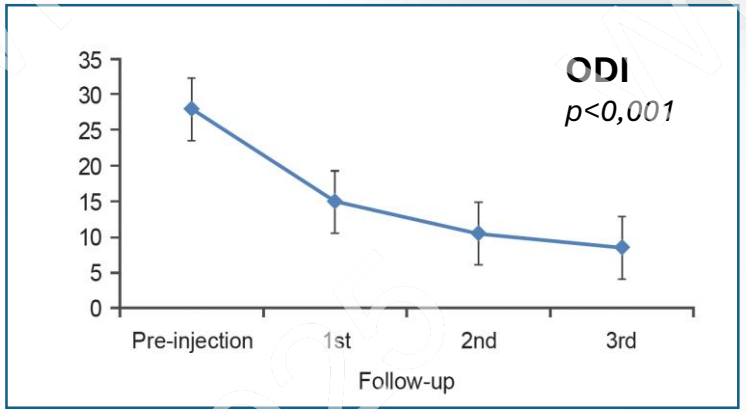
Moderate to severe low backache with radiation to unilateral lower limb of at least 6 weeks duration

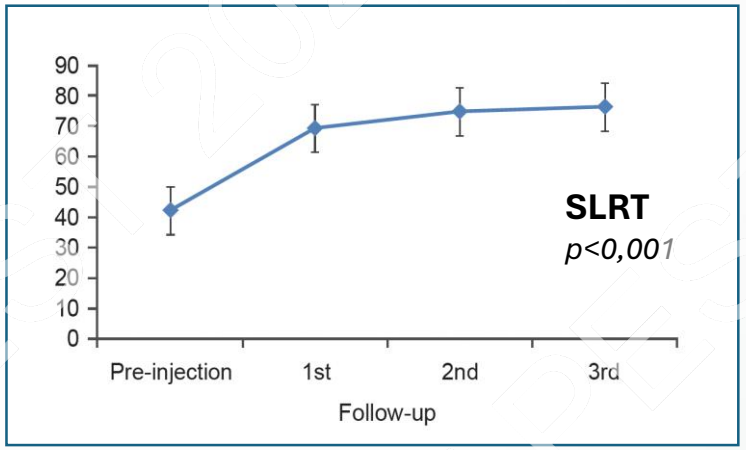
ACS foraminal epidural injection

Average 2 injections at 7 days interval

Evaluated at 3 weeks, 3 months, and 6 months



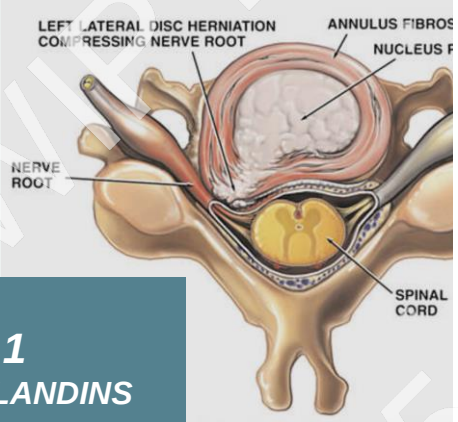




Conclusions

ACS can modify disease course in addition to reducing pain, disability and improving general health. Further studies are needed to confirm the results obtained and to understand the mechanism of the action. Further evaluations also required for long-term symptom improvement or the disease modifying properties of ACS in LBP.

Two groups: 40 PATIENTS
- ACS GROUP (20)



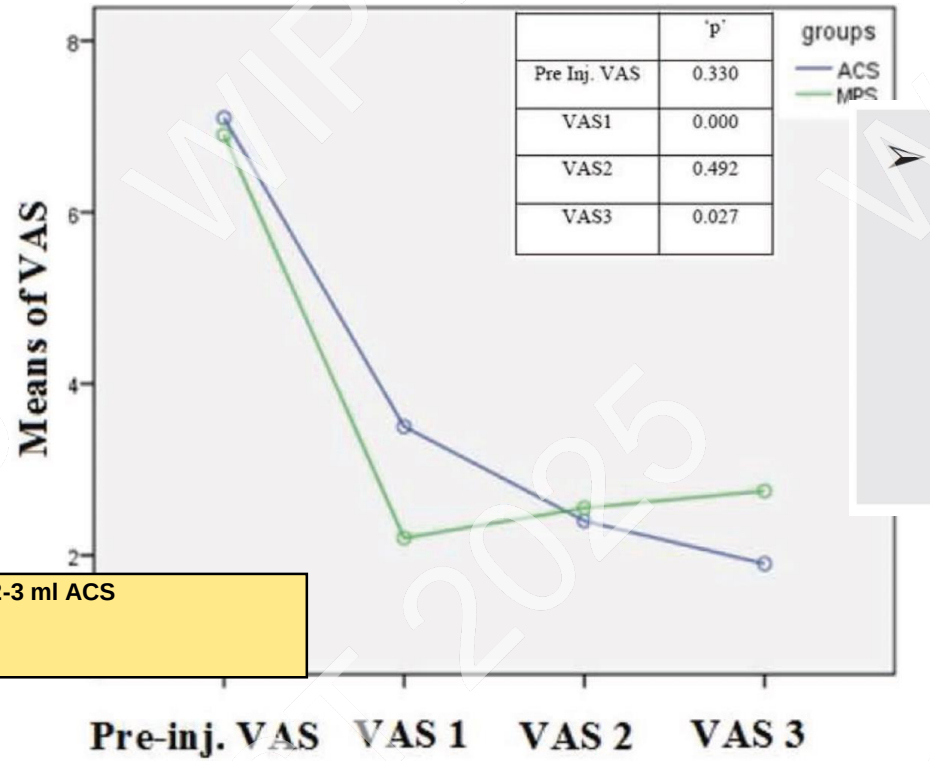
IL- 1
PROSTAGLANDINS

IL-1 rA

- **Contrast dye . Fluoro view. Adm 2-3 ml ACS**
- **1 SESSION**

UNILATER
CONSERVATIVE MEASURES NOT SU

PAIN >6 WEEKS
VAS > 7 / 10
SPURLING TEST ++
RADIOLOGIC CONFIRMATION (MRI)



	'p'
Pre Inj. VAS	0.330
VAS1	0.000
VAS2	0.492
VAS3	0.027

Figure 5. Line diagram summarizing the trend of improvement in VAS between the 2 groups at the 3 follow-ups. VAS indicates visual analogue scale.

, pp E915-E921
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Key Points

- ACS is source of IL-1 receptor antagonist.
- ACS produces sustained improvement in symptoms in patients of cervical radiculopathy.
- The improvement in symptoms produced by image guided injection of ACS is sustained and of longer duration than produced by similarly administered injection of methyl prednisolone.

PAIN RELIEF AT 6 MONTHS:

ACS GROUP: 73,8%
METILPREDNISOLONE GROUP: 58,5%

DOI: 10.5312/wjo.v15.i9.870 ISSN 2218-5836 (online)
SYSTEMATIC REVIEWS

Conservative management of spinal pathology with autologous conditioned serum: A systematic review of the literature

Christian J Rajkovic, Matthew L Merckling, Alyssa W Lee, Galadu Subah, Aryan Malhotra, Zachary D Thomas, Sabrina L Zeller, John V Wainwright, Merritt D Kinon

6 studies. 684 patients

Mechanical lumbar or cervical/lumbar radicular pain

Lumbar spine treatments, 567 patients (82,9%)
- Lumbar radiculopathy, 67 patients
- Degenerative disc disease, 372 patients

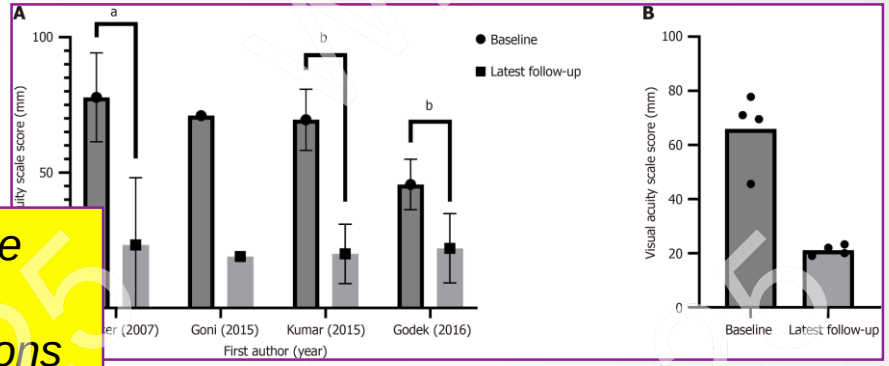
Significant pain reduction *at final follow-up compared to baseline*

Comparable or superior *results to lumbar epidural steroid injections*

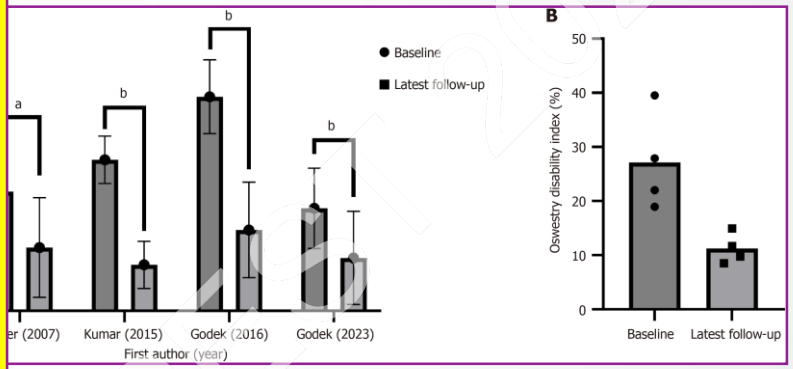
No serious adverse events *were reported*

*The **future** of spine care can benefit from the **inclusion** of ACS in the treatment algorithm of nonoperative management*

Future research is needed *to compare and recommend specific ACS treatment protocols with long term outcome data*



VAS



Oswestry

STUDY PROTOCOL Open Access

Efficacy of conditioned autologous serum therapy (Orthokine®) on the dorsal root ganglion in patients with chronic radiculalgia: study protocol for a prospective randomized placebo-controlled double-blind clinical trial (RADISAC trial)

Marta Homs[1*], Raimon Milà[2], Ricard Valdés[1], David Blay[3], Rosa Maria Borràs[1] and David Parés[4]

2024

Preliminary study protocol

PRF + ACS
VS 2-3 injections (each 14 days)
PRF + SSF

Patients with persistent lower limb radiculalgia
> 6 months

Pain (NPRS)
Functional improvement (ODS)
Quality of life

Follow-up: Baseline, 1 month, 3 months, 6 months, 12 months

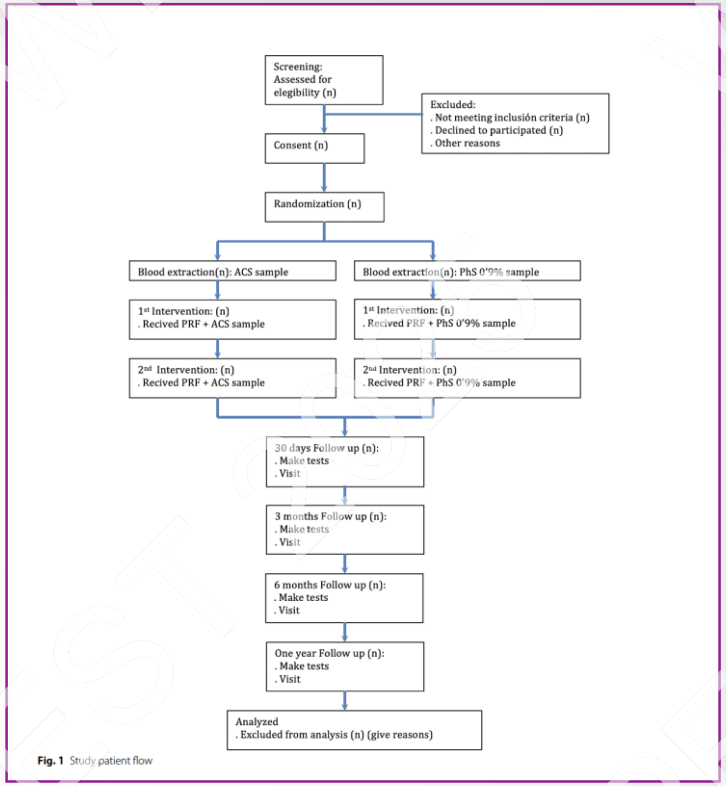


Fig. 1 Study patient flow

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Table 1 Inclusion and exclusion criteria

inclusion Criteria	Exclusion Criteria
1. Patient over 18 years of age, not illiterate. 2. Unilateral, mono and/or bisegmental radicular pain of a lower extremity of at least more than 6 months duration. 3. If you have received treatment before, at least 3 months must have passed since the last therapy received (infiltration, radiofrequency or surgery) and the pain should persist in the same area. 4. Submit Lumbar Magnetic Resonance Imaging (MRI), Electromyography (EMG) performed concomitantly to the pain presented by the patient at the time of inclusion in the study.	1. Refusal of the patient to participate in the study or not to sign the informed consent 2. Allergy to intravenous iodinated contrast and/or local anesthetics. 3. Inability of the patient to maintain the prone position. 4. Systemic or local infection at the puncture site. 5. Present any of the following symptoms: atypical radiation pattern, bilateral involvement, involvement of more than two segments or roots. 6. Concomitant pathological clinical history during the study/therapy: oncological disease, vertebral fractures, myelopathy, systemic disease, connective tissue disease, coagulation disorder, multiple sclerosis, osteomyelitis, or bone edema. 7. Pregnancy or lactation 8. Previous treatment with placement of spinal cord neurostimulator 9. Previous treatment with a brain stimulator for the treatment of epilepsy or Parkinson's disease. 10. Cardiac pacemaker carrier. 11. Patient who does not attend any of the treatment sessions for unjustified reasons.

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