REGENERATIVE MEDICINE FOR SPINE CONDITIONS

San Diego Orthobiologics Medical Group

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DISCLOSURE

Terumo BCT, Advisor

No conflict of interest related to my presentation

- Board Certified in Physical Medicine and Rehabilitation
- Board Certified in Pain Medicine

- Fellowship trained in Interventional Pain and Spine
- Fellowship trained in Orthobiologics and Regenerative Medicine

- 15 years clinical practice
- Clinical trials – PRP and Bone marrow cells in Spine, Adipose stem cells for knee osteoarthritis
- Author – clinical research, book chapters, articles in Regenerative Medicine
- Faculty and Speaker - TOBI, IOF, AAPM&R, Orthoregen, MSK Ultrasound and Orthobiologics, etc
- Academic affiliations: UCSD, UCLA, Western Univ of Health Sciences, SCU Sports Medicine

ORTHOHEALING METHOD™
CERTIFIED PROVIDER

Interventional Orthobiologics Foundation

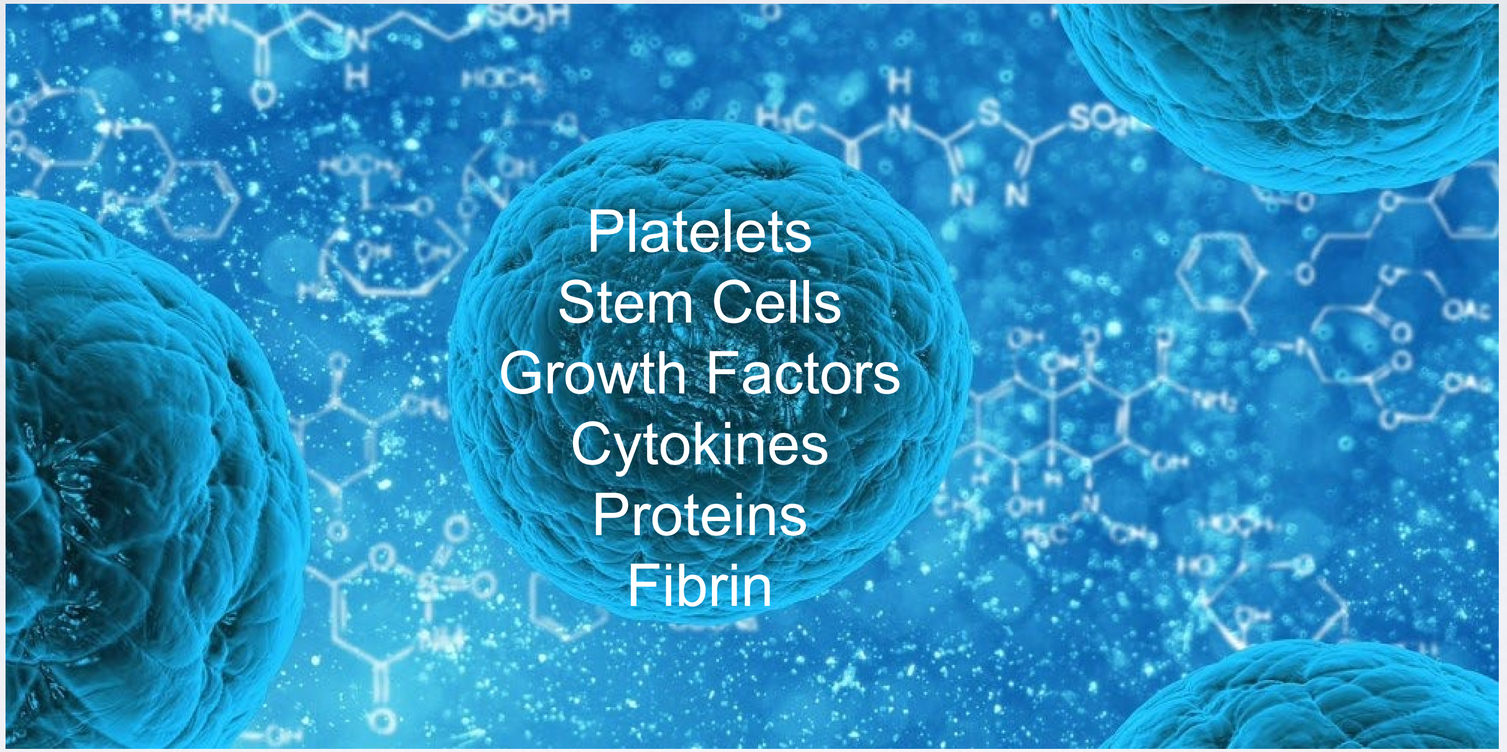
AMERICAN BOARD OF PAIN MEDICINE
ABPM

aaPM&R
American Academy of Physical Medicine and Rehabilitation

- WHAT BIOLOGIC INJECTIONS IN THE SPINE ARE SUPPORTED BY RESEARCH ?
- ARE THESE INJECTIONS SAFE AND EFFECTIVE ?
- A PARADIGM SHIFT ?

ORTHOBIOLOGICS

Cells or substances derived from cells that are used for the treatment of orthopedic conditions



Augment body’s healing mechanisms and repair damaged tissues

PLATELET RICH PLASMA (PRP)

- Volume of autologous plasma with a platelet concentration above baseline
- Contains amplified amounts of growth factors, cytokines, and other mediators thought to accelerate healing process

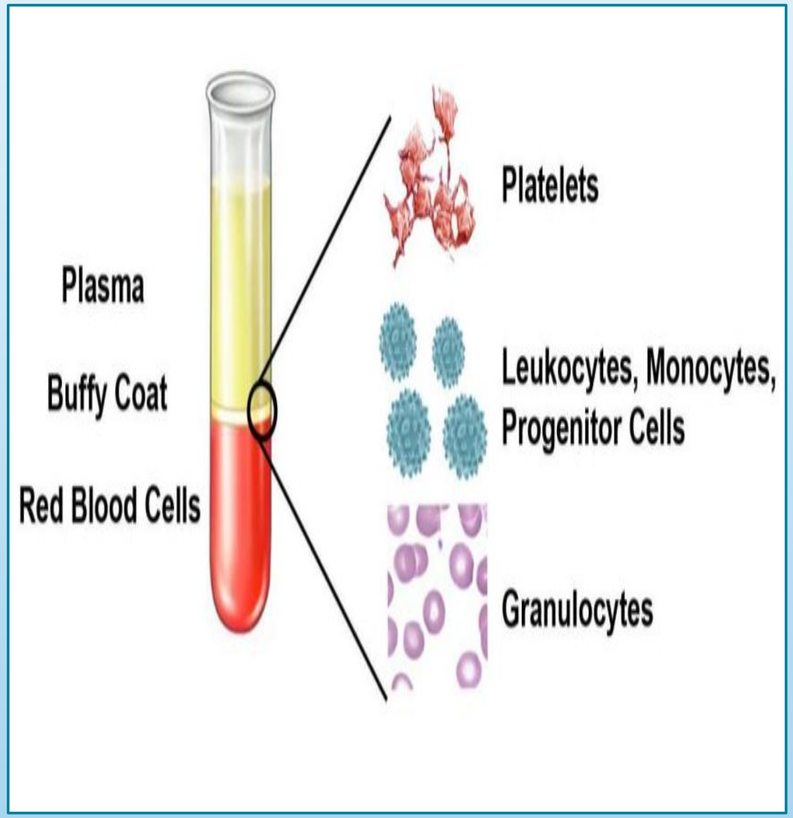


Image adapted from Theodore Sand, Ph.D.

Table 1
Key regenerative growth factors stored in platelet alpha granules and their functions

Growth Factor	Function
PDGF	Stimulates cell proliferation, chemotaxis, and differentiation Stimulates angiogenesis
TGF-β	Stimulates production of collagen type I and type III, angiogenesis, re-epithelialization, and synthesis of protease inhibitors to inhibit collagen breakdown
VEGF	Stimulates angiogenesis by regulating endothelial cell proliferation and migration
EGF	Influences cell proliferation and cytoprotection Accelerates re-epithelialization Increases tensile strength in wounds Facilitates organization of granulation tissue
bFGF	Stimulates angiogenesis Promotes stem cell differentiation and cell proliferation Promotes collagen production and tissue repair
IGF-1	Regulates cell proliferation and differentiation Influences matrix secretion from osteoblasts and production of proteoglycan, collagen, and other noncollagen proteins

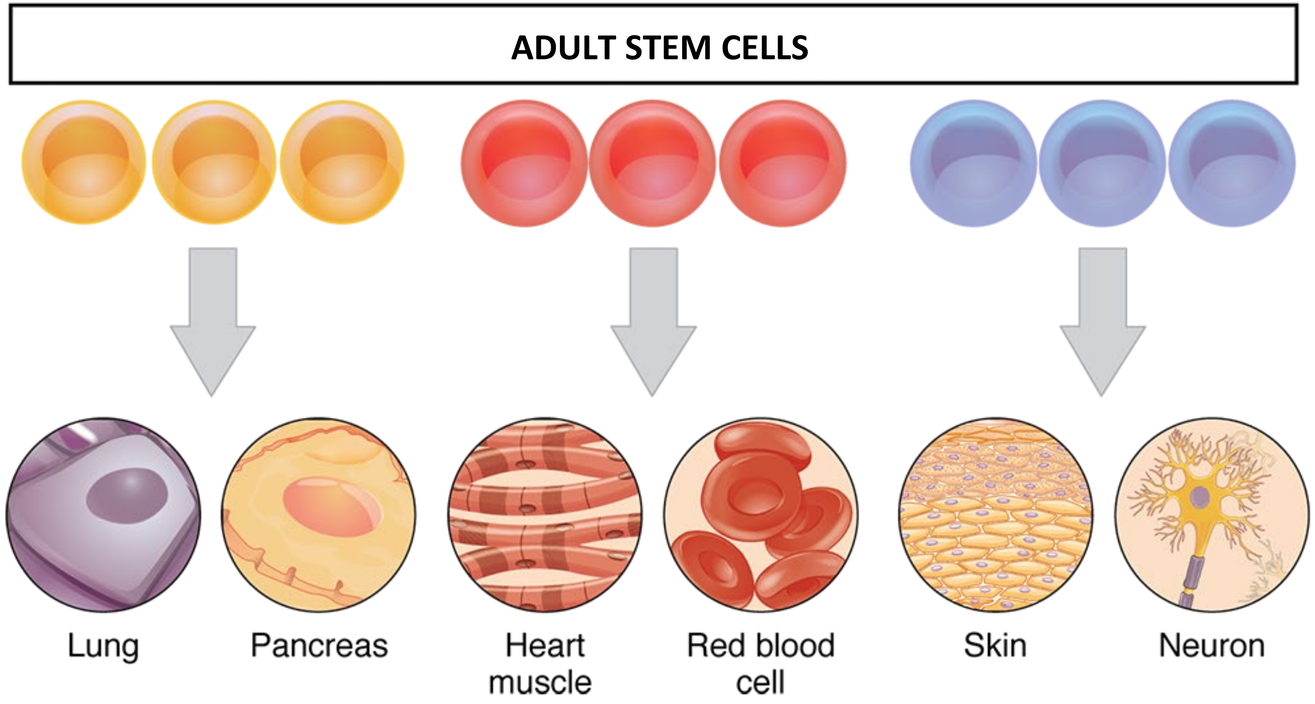
Abbreviations: PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; IGF-1, insulin-like growth factor.

Wu, et al. Phys Med Rehabil Clin N Am 27 (2016)

CELL BASED THERAPIES

BONE MARROW

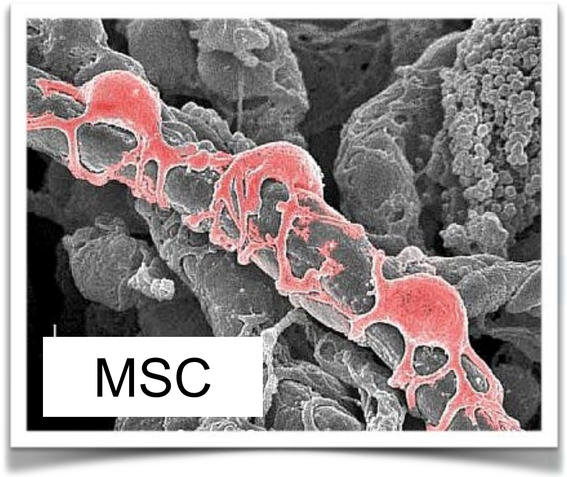
ADIPOSE TISSUE



MESENCHYMAL STEM CELLS (MSC)

specific type of adult stem cells
that can differentiate into bone, tendon, cartilage, muscle cells

https://commons.wikimedia.org/wiki/File:422_Feature_Stem_Cell_new.png



MSC

Activated

Anti-Scarring
KGF, SDF-1, MIP-1a & 1b

Anti-Apoptotic
STC-1, SFRP2, TGF-β1, VEGF, HGF

Angiogenic
VEGF, TGF-β1

Mitogenic
TGF-α, TGF-β, HGF, IGF-1, FGF-2, EGF

IL-6, IL-8, IL-10, IL-1RA, PGE2, IDO, TGF-β1, HGF, TSG-6, STNF-R, NO, sHLA-G5

LL-37, IDO

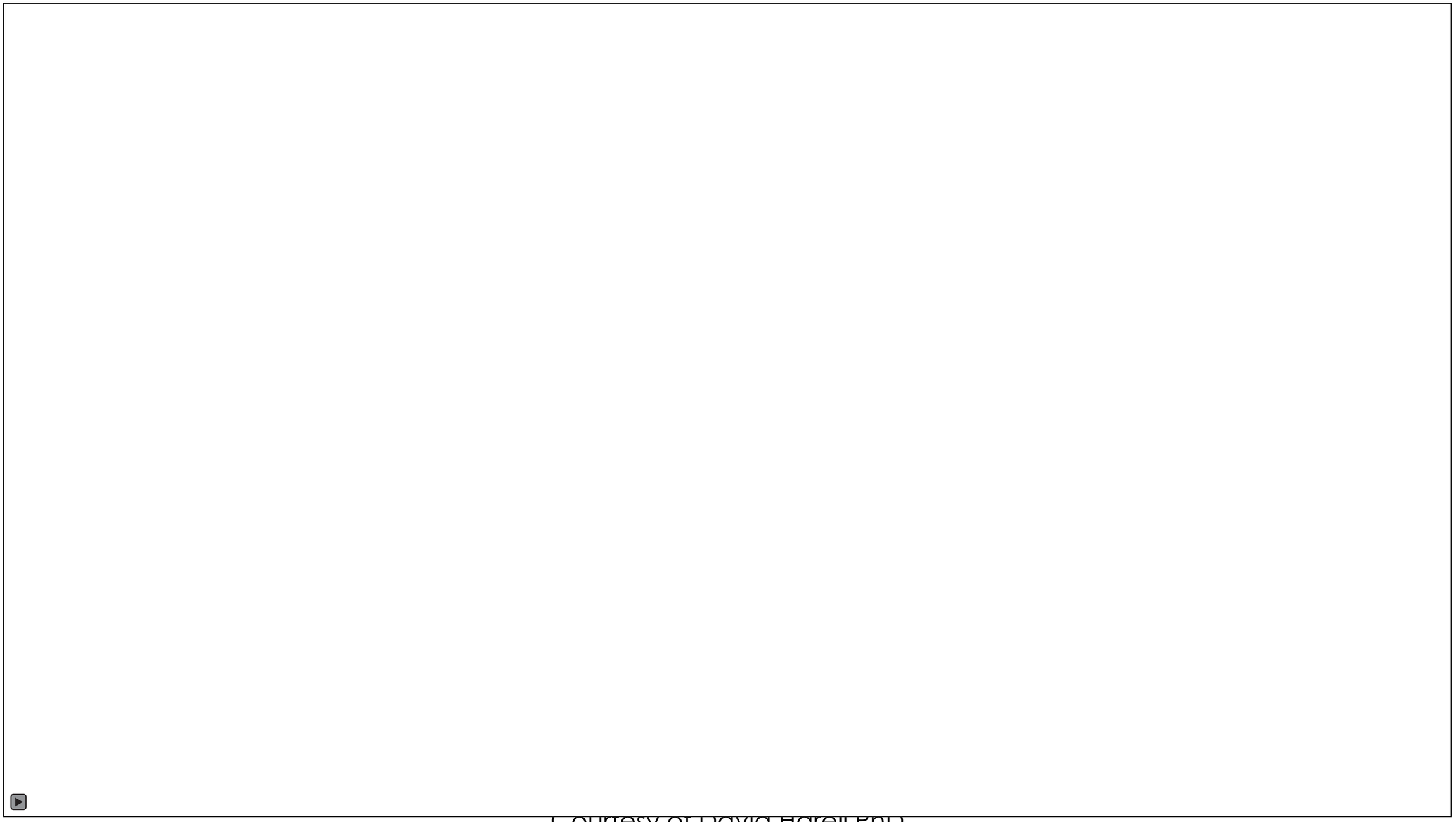
HEAL TISSUE

CONTROL INFLAMMATION

FIGHT INFECTION

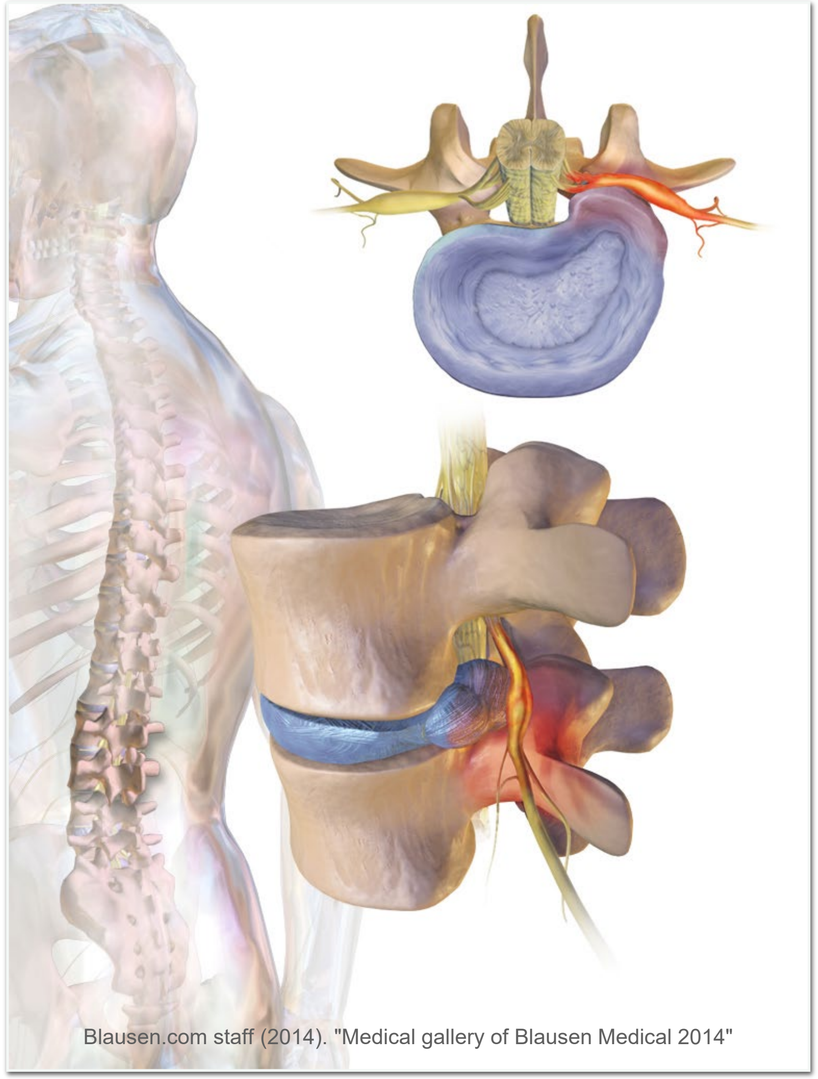
RELEASE OF MOLECULES

Adapted from A. Caplan



Courtesy of David Harell PhD

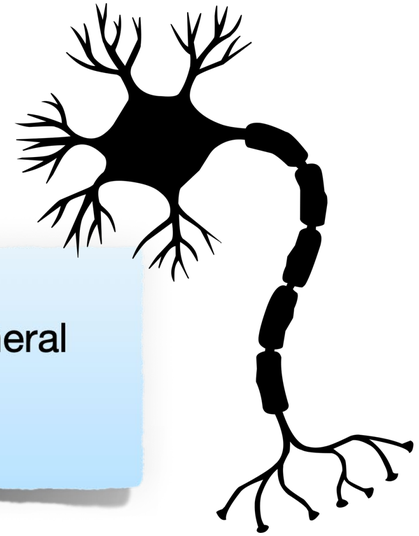
BIOLOGICS FOR RADICULOPATHY



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014"

BIOLOGICS FOR NERVE INJURY

IN VIVO AND IN VITRO STUDIES



- Platelet derived growth factor (PDGF-B) induces peripheral nervous system regeneration

  - *Oya et al. Glia 2002.*

- Insulin-like growth factor (IGF-1) possess neurotrophic activities and stimulates peripheral nerve regeneration.

  - *Kanje et al. Brain Research 1989.*

- Potential of PRP in remyelination, axonal regeneration, and angiogenesis of injured peripheral nerves.

  - *Giorgetti et al. Neural Regen Res 2015.*

- PRP can regenerate axons through short nerve gaps and longer nerve gaps 2-12 cm (with conduit).

  - *Kuffler et al. Progress in Nuerobiology 2013.*

- IL-1Ra improved neurophysiologic parameters and clinical symptoms of polyradiculoneuropathy in rats induced with experimental allergic radiculitis.

  - *Wehling P, et al .Spine 1996*

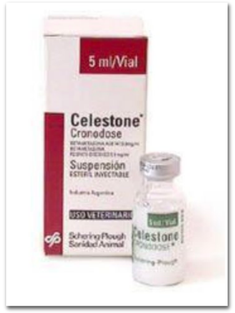
- PRP promotes axon growth in spinal cord tissues through mechanisms associated with insulin-like growth factor (IGF-1) and vascular endothelial factor (VEGF).

  - *Takeuchi et al. Neuroreport 2012.*

EPIDURAL BIOLOGIC STUDIES

STUDY	LEVEL OF EVIDENCE	DETAILS	BIOLOGIC	RESULTS
BECKER et al. 2007	I	• Prospective double blind reference controlled • ACS vs 5mg vs 10mg triamcinolone • N:84 Follow up: 6 mos	ACS x 3 1 wk apart Interlaminar	• VAS: ACS grp was superior to both steroid grps up to 22 wks • ODI: No significant difference
RUIZ-LOPEZ et al. 2020	I	• Prospective randomized controlled double-blinded • PRP vs 60 mg celestone • N:50 Follow up: 6 mos	LR-PRP x 1 Caudal	• VAS: PRP grp had significantly reduced VAS sustained at 3 & 6 months • SF-36 : PRP grp had significant improvement in 5 domains vs. steroids which only showed improvement in the bodily pain domain.

VS



EPIDURAL BIOLOGIC STUDIES

STUDY	LEVEL OF EVIDENCE	DETAILS	BIOLOGIC	RESULTS
KUMAR et al. 2015	IV	• Prospective Case series • N: 20 Follow up: 6 mos	ACS x 1-3 7 days apart 2ml Interlaminar	Significant difference in VAS, ODI, SF-12 physical & mental component
BHATHIA et al. 2016	IV	• Prospective Case series • N:10 Follow up: 3 mos	PRP x 1 5 ml Interlaminar	All improved in VAS, SLR, ModODI Q
CENTENO et al. 2017	IV	• Prospective registry • N:470 Follow up: 2 yrs	Platelet lysate 50% 4% lidocaine 25% 100-200 ng/ml hydrocort 25% 3-5 cc IL or TF	• NPS:Ave pain change at each time point is stat. lower than baseline • FRI:Ave change score exceeded the MCID beyond 1month • Mod SANE: Ave rating showed 49.7% improvement at 24 months
CORREA et al. 2019	IV	• Prospective, observational, non randomized • N:250 F/U: 2 yrs	PRGF x2 6-8 wks apart 10-12 ml Interlaminar	• Significant improvements in Mean VAS and Mean MACNAB score through 2 years • MRI improvements in a few pts

SAFETY OF EPIDURAL PRP

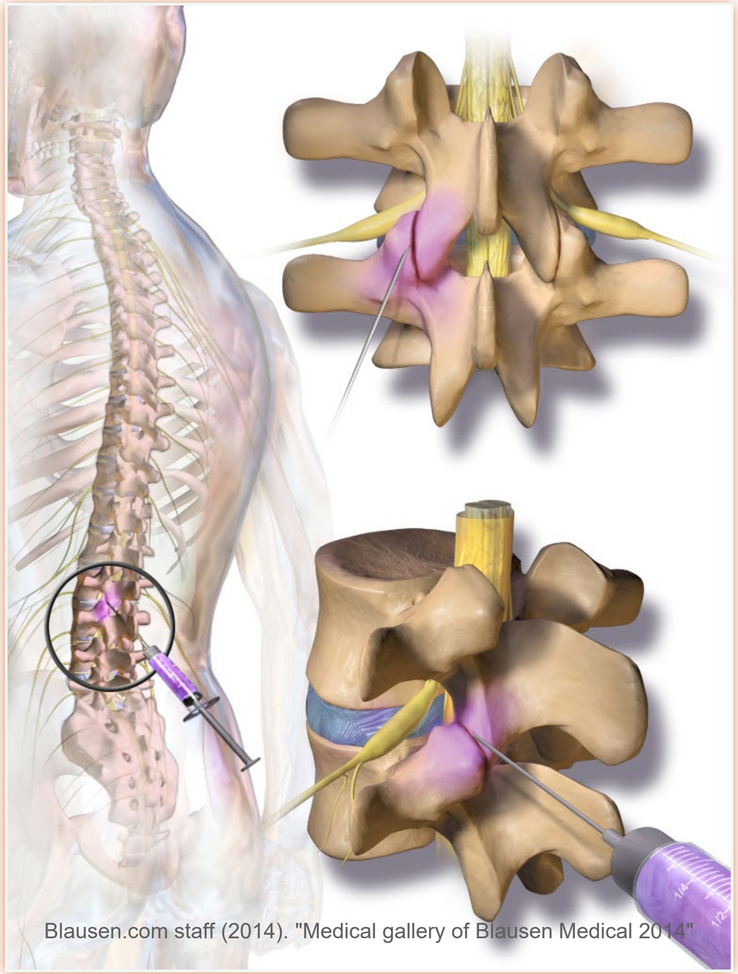
SIX STUDIES, 884 PATIENTS, 2 YRS FOLLOW UP

NO SERIOUS ADVERSE EFFECTS OF INFECTION, NEUROLOGIC DEFICIT OR HOSPITALIZATION

Minor complications are largely procedural related and transient:

Severe HA in 1 pt	Becker Study
Syncope, HA, sweating, tachycardia in 5 pts (20%) Back stiffness in 1 pt (4%)	Kumar Study
Inflammation, soreness, stiffness, numbness - 23 (4.8%) N/V, positional HA, lightheadedness - 3 (0.63%) Redness, swelling - 3 (0.63%)	Centeno Study

BIOLOGICS FOR FACET JOINT PAIN



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014"

BIOLOGICS FOR INTRA-ARTICULAR USE

PRE-CLINICAL STUDIES

Increase in chondrocyte and cell matrix proliferation

Inflammation Modulation

Recruitment of other cells into the damaged tissues, triggering the healing response

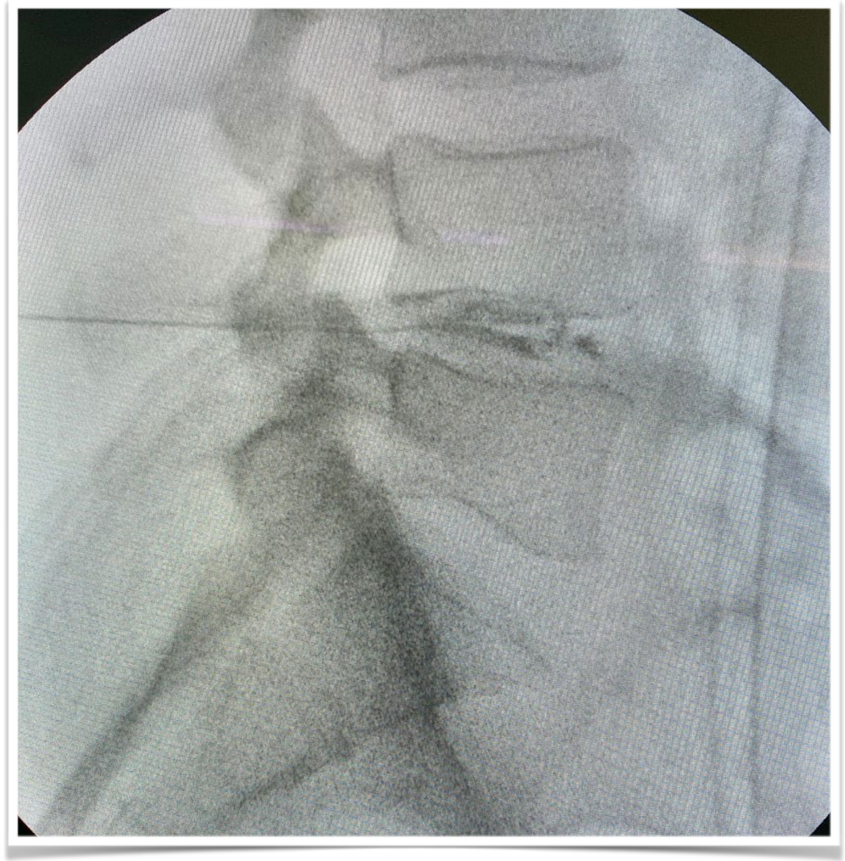
Analgesic effect

Filardo et al. Knee Surg Sports Traumatol Arthrosc (2015)

FACET JOINT BIOLOGIC STUDIES - PRP

STUDY	LEVEL OF EVIDENCE	DETAILS	BIOLOGIC	RESULTS
WU et al 2016	IV	• Prospective Series • N- 19 • Follow-up: 3 months	PRP 0.5 cc vol 4-5x concentration	• Significant improvement in VAS, ODI and RMDQ • 79% of the patients reported “good” or “excellent” outcomes • No adverse events
WU et al 2017	I	• Prospective Randomized Controlled • PRP vs Lidocaine + Steroid • N-46 • Follow-up: 6 months	PRP 0.5 cc vol 4-5x concentration	• Significant improvement in VAS, ODI and RMDQ in both groups at 1 month • Only PRP group sustained improvement in 6 months • No severe treatment-related complications or adverse events.

INTRADISCAL BIOLOGICS



PRE-CLINICAL STUDIES

INTRADISCAL PRP

- nucleus pulposus proliferation
- restoration of normal cellular architecture and disc height
- increased disc hydration
- decrease in inflammatory cells

1. Paglia et al. Spine 2016
2. Cho et al. Artificlal Organs 2016.
3. Gullung et al. Evid based Spine Care J.2011

INTRADISCAL BONE MARROW CELLS

- enhanced matrix production
- NP proliferation and MSC differentiation to chondrogenic lineage
- increased disc hydration and disc height

1. Le Maitre, et al.Arthritis Res Ther 2009.
2. Sakai, et al. Biomaterials.2006
3. Yim et al. Stem Cells Dev 2104.

INTRADISCAL PRP STUDIES

Study	Tuakli et al. 2016 [31]	Comella et al. 2017 [32]	Akeda et al. 2017 [33]	Levi et al. 2016 [34]
Type of study	Prospective, double-blind randomized controlled study	Case Series	Case Series	Case Series
Level of evidence	II	IV	IV	IV
No. subjects	29	15	14	22
PRP Volume Injected (ml)	1-2	1	2	3
Platelet Concentration	NR	NR	3.7 x baseline	NR
Follow-up (months)	12	6	10	6
Outcomes	VAS, FRI, SF-36 pain, SF-36 physical function	VAS, PPI, ODI	VAS, RDQ	VAS, ODI

Hirase, et al. Cureus. Jun 2020.

INTRADISCAL BONE MARROW CELLS

Study	Orozco et al. 2011	Yoshikawa et al. 2010	Pettine et al. 2017	Mochida et al. 2015	Noriega et al. 2017	Centeno et al. 2017	Elabd et al. 2016
Type of study	Case Series	Case Series	Case Series	Case Series	Prospective randomized control study	Case Series	Case Series
Level of evidence	IIA	IV	IV	IV	II	IV	IV
Country	Spain	Japan	USA	Japan	Spain	USA	USA
No. subjects	10	2	26	9	12	33	5
Amount injected	$5x10^6$ cells per disc from a suspension containing 10^7 cells/ml	10 ml of 10^5 cells/ml in combination with collagen sponge	2-3 ml per disc; $1.2x10^8$ cells per ml	$1x10^6$ cells/702 μL sterile saline per disc	$25x10^6$ cells per disc from a suspension containing 12.5 x 10^6 cells/ml	1-3 ml per disc; avg $2.3x10^7$ cells per disc	0.25-1 ml per disc; avg 30.8 x 10^6 cells per disc
Follow-up (months)	12	24	36	36	12	72	72
Outcomes	ODI, VAS, SF-36	VAS, JOA	ODI, VAS	JOA	ODI, VAS, SF-12	VAS, FRI, SANE	QOL Questionnaire

Hirase, et al. Cureus. Jun 2020.

Wolff *et al. BMC Musculoskeletal Disorders* (2020) 21:135
https://doi.org/10.1186/s12891-020-3126-7

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Injections of concentrated bone marrow aspirate as treatment for Discogenic pain: a retrospective analysis

Michael Wolff[1*], Jon Mark Shillington[1], Christopher Rathbone[2], Shawn K. Piasecki[3] and Brian Barnes[3]

Thirty-three patients

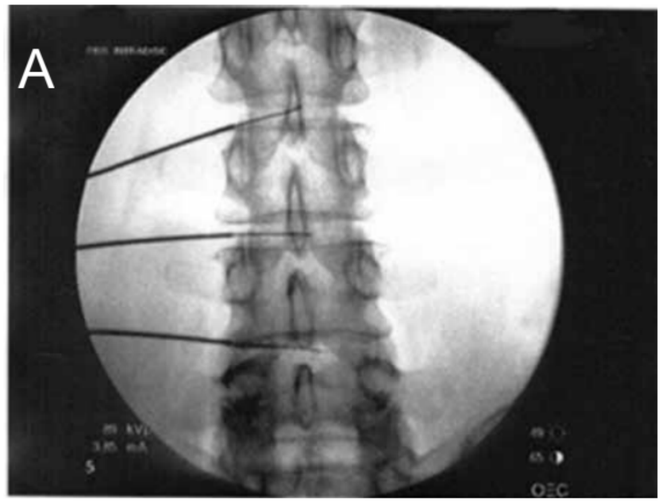
12 months

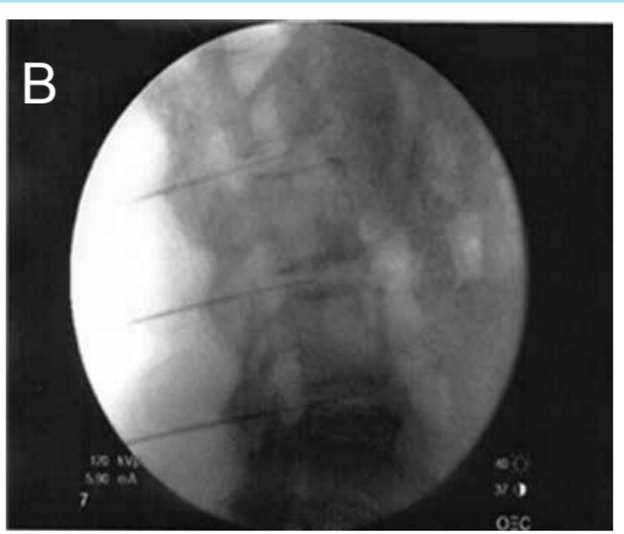
41% of patients had at least 50% improvement in NRS
30% of patients had at least 50% improvement in SF-36
36% of patients had at least 50% improvement in ODI

Biologics for Lumbar Discogenic Pain: 18 month follow up for safety and efficacy

Navani, Ambach, et al. Interventional pain mgmt reports 2018

- Case series 20 pts
- PRP for less degenerated disc
- BMC for more degenerated disc





Biologics for Lumbar Discogenic Pain:18 month follow up for safety and efficacy. Interventional Pain Management Reports, 2018; 2(3): 111-118.

Biologics for Lumbar Discogenic Pain: 18 month follow up for safety and efficacy

Navani, Ambach, et al. Interventional pain mgmt reports 2018

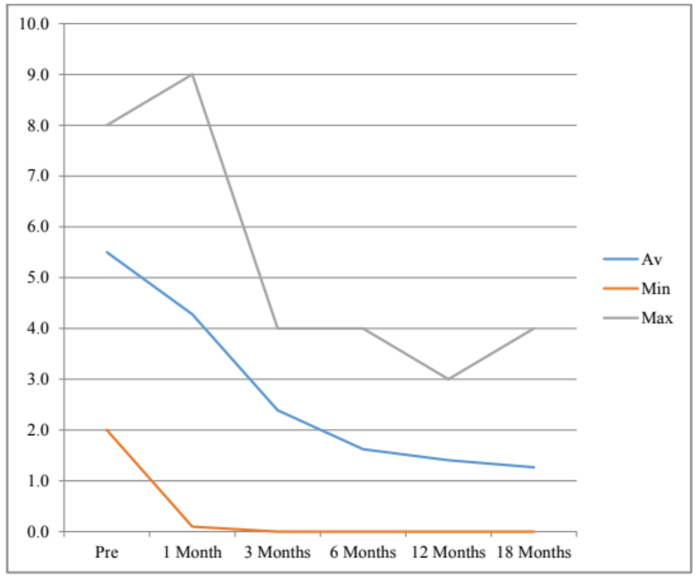


Fig. 4. Change in VPS over the 18 months follow-up.

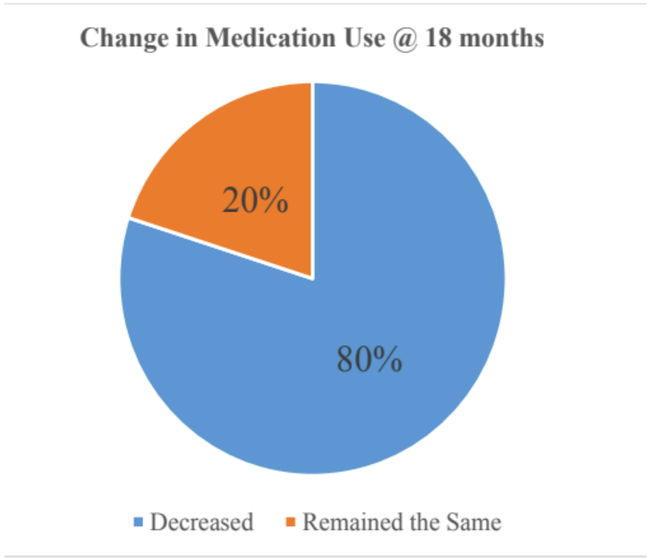
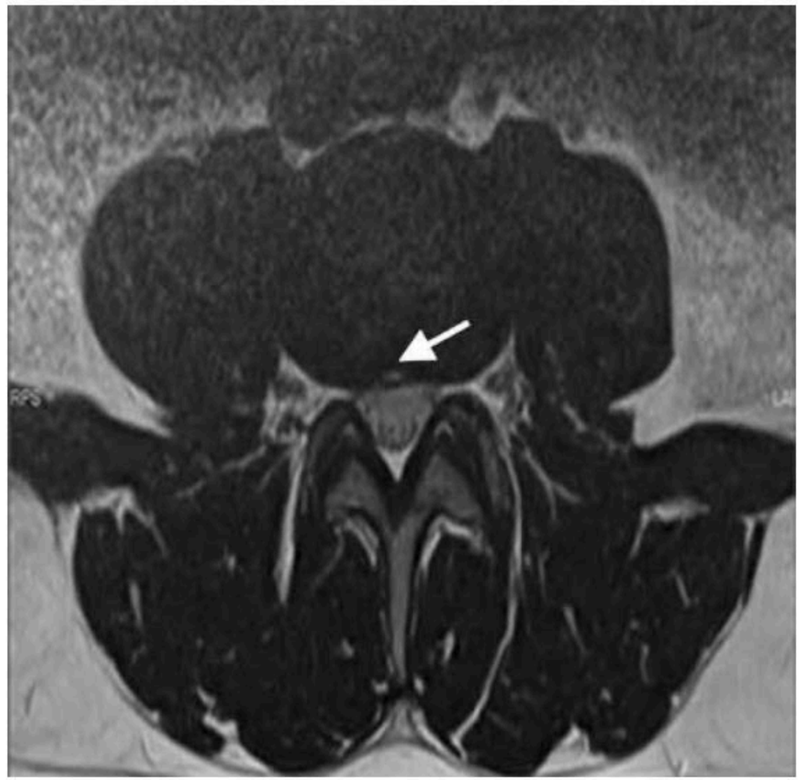


Fig. 5. Change in medication usage at 18 months follow-up.

- 93% of pts showed >50% pain relief (VPS) and improvement in function (SF 36)
- 80% decreased medication use
- No adverse effects. No ER, hospitalization or surgery.

Biologics for Lumbar Discogenic Pain: 18 month follow up for safety and efficacy

Navani, Ambach, et al. Interventional pain mgmt reports 2018



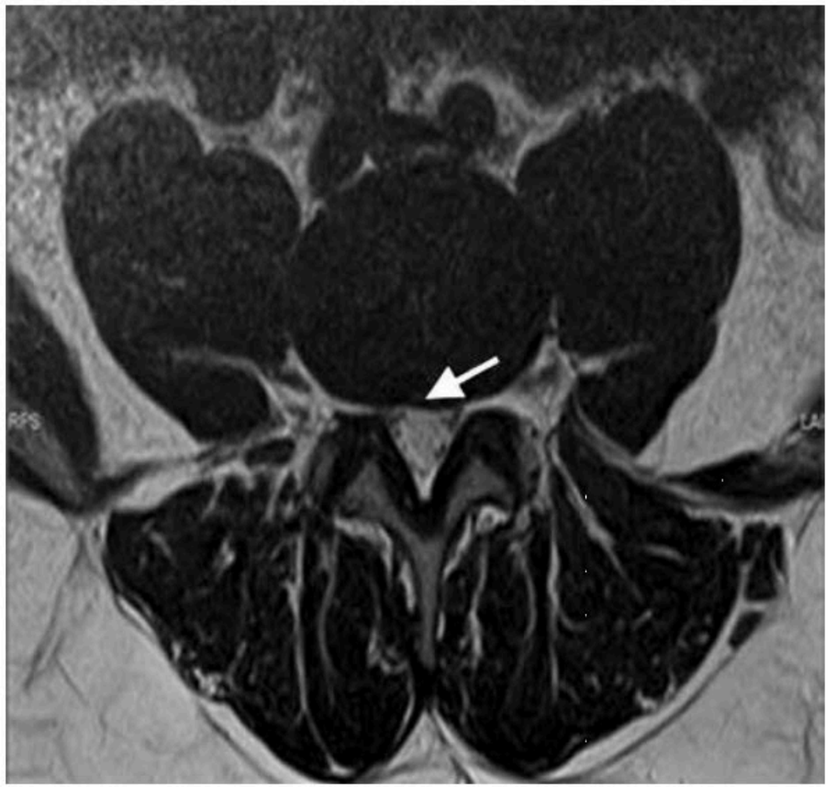


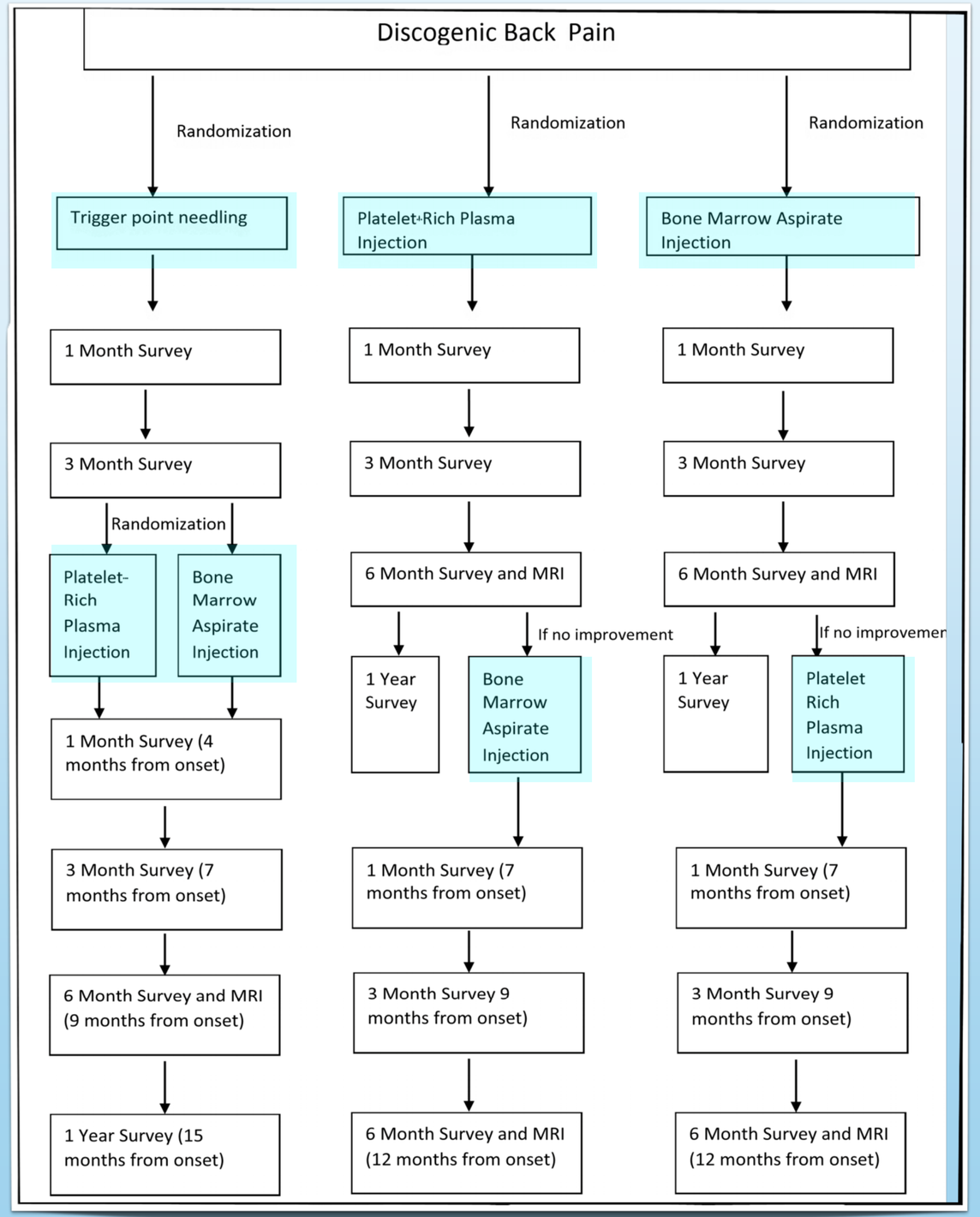
Fig. 6. Axial T2 MRI images identifying resolution of posterior annular tear at L3-4 disc 6 months post PRP injection.

Multicenter Randomized Placebo-Control Trial of PRP vs BMAC for Lumbar Disc Disease

Navani, Ambach, Calodney, Rosenthal

- Prospective, randomized, placebo controlled, multi center pilot study
- Total 40 patients included in analysis
- NRS pain, ODI disability & NASS satisfaction at 1,3,6,12 mos

ClinicalTrials.gov Identifier: NCT04102761



RESULTS

- **PRP and BMC were equally effective in treating discogenic low back ad/or leg pain after 12 months of a single injection**
- All placebo patients crossed to a biologic intervention at 3 months
- All crossed patients showed significant improvement in NRS, ODI and NASS scores
- No secondary biological intervention was indicated in any of the patients
- No complications

SAFETY OF INTRADISCAL BIOLOGICS

PRP

- Safety shown in clinical studies of at least 2 years
- 2 out of 90 (2%) patients had transient lower extremity paresthesia

  - Systematic Review, mean follow up 8 mos +/- 3.6 mos
- Published Case report of Spondylodiscitis (C. Acnes) after LP-PRP injection

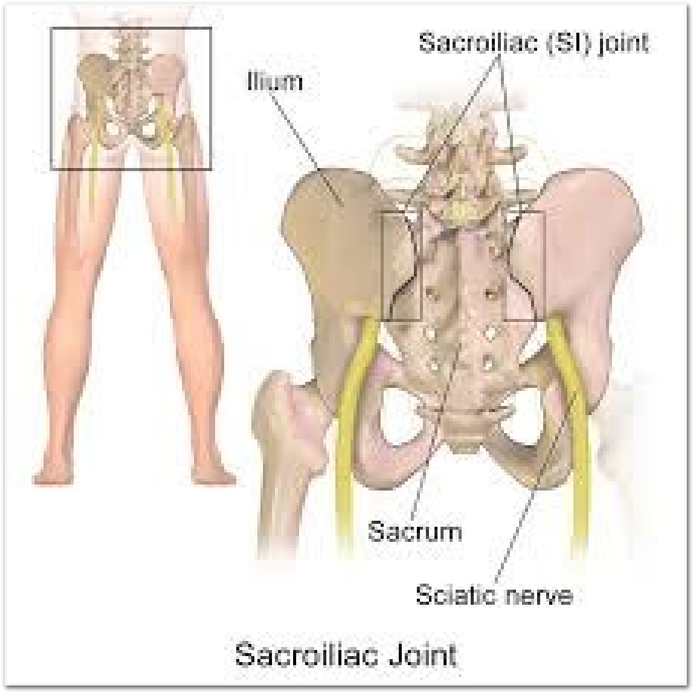
Bone marrow cells

- Safety shown in clinical studies of up to 6 years
- One patient out of 90 (1.0%) experienced herniated nucleus pulposus (HNP)

  - Systematic Review : 97 patients, mean follow-up 44.4 +/- 25.4 months

Hirase et al. Cureus. Jun 2020
Cheng et al. Regenerative Med. Aug 2019
Beatty et al. Regenerative Medicine. Aug 2019
El-Kadiry, et al. Frontiers in Medicine. Mar 2021.

PRP for Sacroiliac (SI) joint pain



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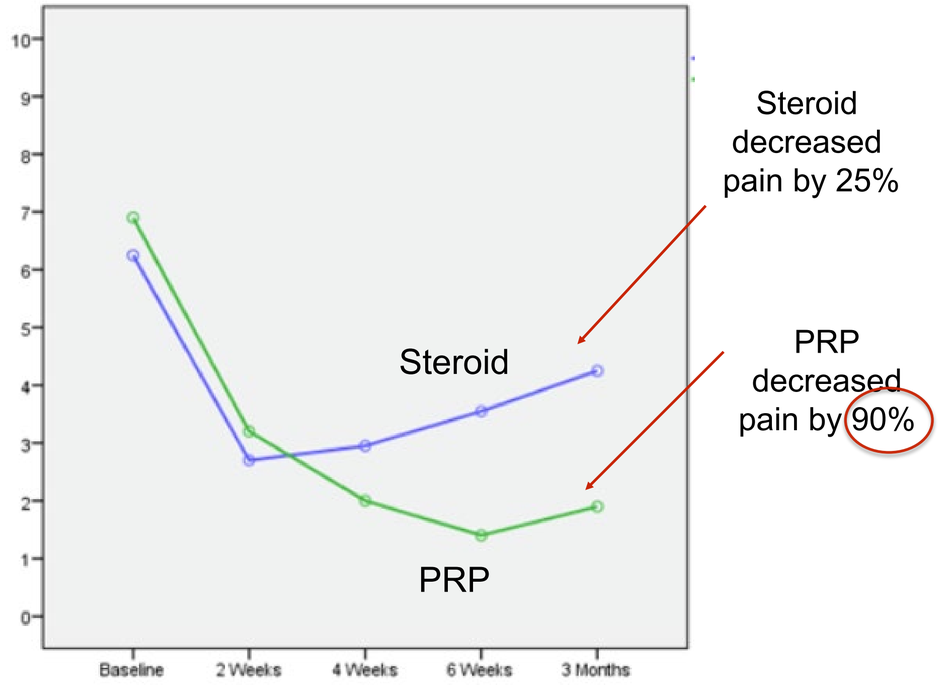
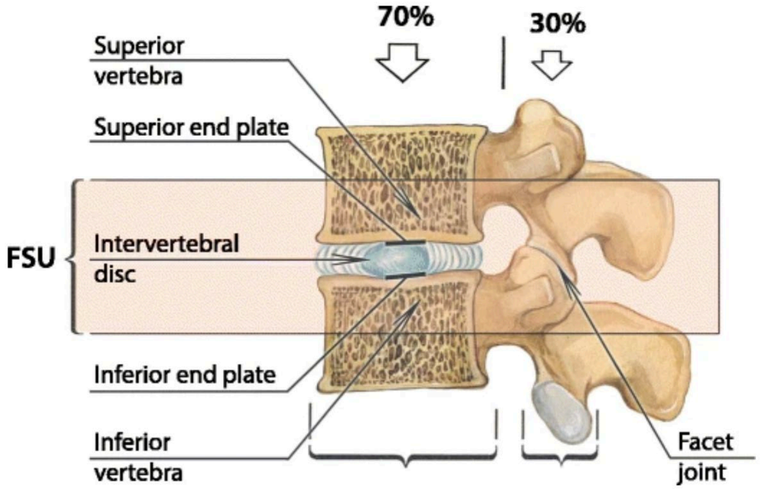


Pain and function improved significantly greater and lasted longer in the PRP group

No serious adverse events

Singla et al. Pain Pract 2017

FUNCTIONAL SPINE UNIT



https://commons.wikimedia.org/wiki/File:Functional_spinal_unit_(FSU).webp

Multiple subsystems that stabilizes the spine. The spine behaves as a function of all its parts

Pain Generator Approach

Knowing What Hurts

Single Structure Injection

Focusing on Parts

PARADIGM SHIFT

ORTHOBIOLOGICS

Regenerative Medicine Approach

Knowing Why it Hurts

Multiple Structure Injection

Treating the Whole Organ

Regen Med. 2022 Jan;17(1):11-22. doi: 10.2217/rme-2021-0019. Epub 2021 Dec 15.

Personalized multitarget biologic injection in the spine: prospective case series of multitarget platelet-rich plasma for low back pain

Edilson S Machado [1 2], Mary A Ambach [3], José Mp Caldas [4], Jason J Wei [5], Markus Bredemeier [6]

PMID: 34907784 DOI: 10.2217/rme-2021-0019

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Low back pain >12 weeks • Failure of conservative treatments (oral medications, physical therapy, steroid injections) • Satisfy criteria for lumbar epidural, facet, intradiscal or paravertebral intramuscular injection

- 46 patients
- Facet joints, intervertebral discs, epidural space, and/or paravertebral muscles
- Follow up 1 year

Regen Med. 2022 Jan;17(1):11-22. doi: 10.2217/rme-2021-0019. Epub 2021 Dec 15.

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RESULTS

- Mean VAS pain : 8.48 to 5.53 at 1 year
- Mean RMDQ function: 8.00 to 10.71 at 1 year
- 54.3% were ‘very satisfied’ and 63.0% would ‘definitely’ repeat the procedure
- Significant decrease in reported medication use at 1 year

Regen Med. 2022 Jan;17(1):11-22. doi: 10.2217/rme-2021-0019. Epub 2021 Dec 15.

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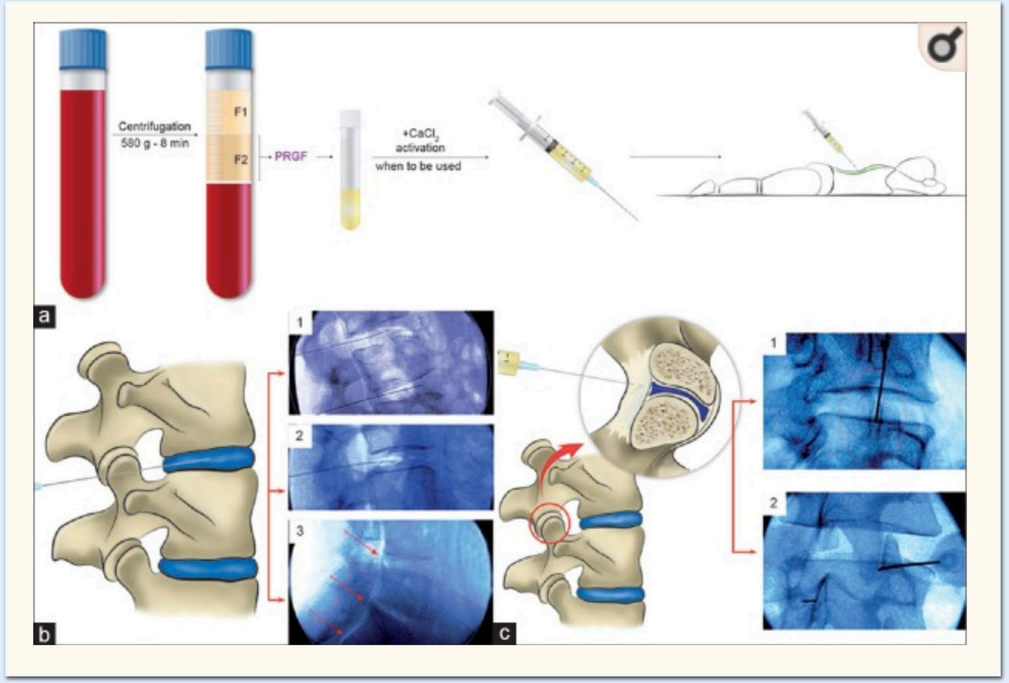
No adverse events of infection, neurologic injury or hospitalizations during the 52 week follow-up period.

Intradiscal + Intra-articular Facet + Transforaminal Epidural PRGF
Retrospective pilot study of 86 patients with chronic LBP

Kirchner and Anitua, 2016



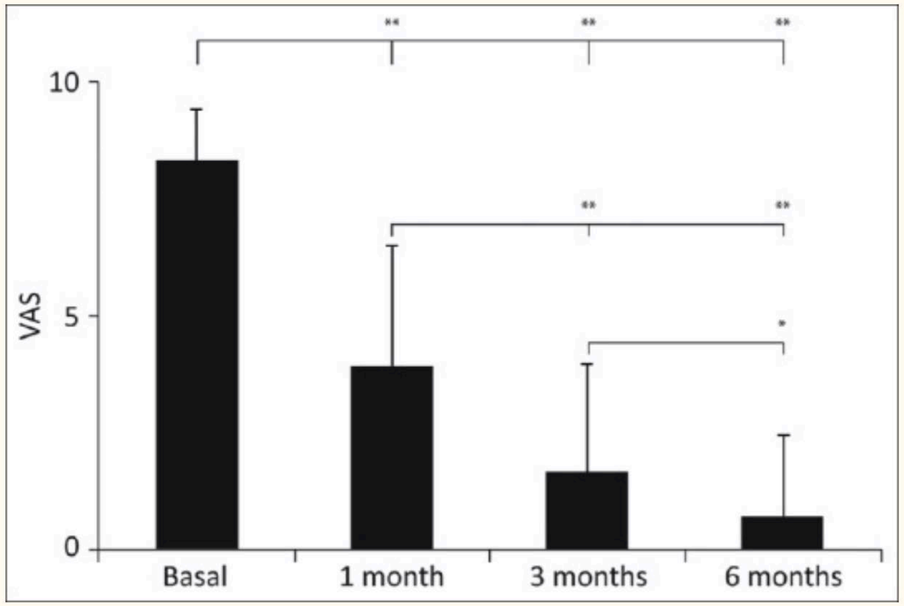


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Figure 2

Graphic representation of the postprocedural pain reduction assessed by visual analog scale showing a statistically significant pain reduction from basal visual analog scale to first, third, and sixth months after the treatment, respectively, with respect to all the time evaluation (**$P < 0.0001$) except for the visual analog scale between the 3rd and 6th month whose signification was lower (*$P < 0.05$)

Significant (VAS) pain reduction

90.7 % showed excellent response (VAS 1-3) at 6 mos

All 3 structures were injected in all patients.

J Carniovertebr Junction Spine 2016
doi:10.4103/0974-8237.193260

ATLURI, IOF conference 2019

- Controlled Prospective Trial
- 70 patients with chronic LBP
- BMC therapy (N=35) vs Traditional therapies (N=35)
- Discs, Facets, Epidurals and SIJ BMC Injection
- 1 year follow up

PRELIMINARY RESULTS:

6 months

- Overall Best Pain 1.86 (BMC) vs 5 (Control)
- ODI 29.3 (BMC) vs 42.8 (Control)
- EuroQol 0.67 (BMC) vs 0.55 (Control)
- No major complications

SYSTEMATIC REVIEW OF THERAPIES FOR LOW BACK PAIN

NC n pain.

ts.

PHARMACOLOGIC: Small to moderate, primarily short-term effects on pain.

Chou R, et al. Systematic Review for an American College of Physicians Clinical Practice 16 Guideline. Ann Intern Med 2017

IS BIOLOGICS THE ANSWER?

PATIENT EDUCATION

Only 16% of 4,655 older adults with back pain

ha **ears**

REALISTIC EXPECTATION

despite multiple spinal interventions.

Jarvik JG et al. Long-term outcomes of a large, prospective observational cohort of older adults with back pain. Spine J. 18(9), 1540-1551 (2018)

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