The Orthobiologic Institute (TOBI): 8th Annual PRP & Regenerative Medicine Symposium Abstracts

ABSTRACT #1

Where Does Prolotherapy Fit in the Treatment of Orthopedic Conditions?

Joanne Borg-Stein, MD. Harvard Medical School, Department of PM&R, Cambridge, MA.

Goals: Basic overview of Prolotherapy, including proposed mechanisms
- Scientific literature to support these treatments
- How to apply Prolotherapy in practice

Conclusion: Prolotherapy Clinical Recommendations 2016: Growing research suggest that prolotherapy is a consideration for:
- CMC/finger OA
- Knee OA
- Sacroiliac pain

When to consider prolotherapy: clinical pearls
- A comprehensive regional approach with a large number of areas to inject.
- When there is concomitant neurogenic inflammation/pain use 5% in a neural prolotherapy style.
- In general, higher (25%) for intra-articular application and 12.5-15% for periarticular structures
- Consider "non inflammatory" 10% in sensitized patients
- Regenerative treatment of choice for in season athletes
- If blood draw is a problem
- In cases of hypermobility or laxity: MDI shoulder, SI post partum; Sequela of chronic ankle sprain
- Up front expense is less and spread out over several months

Patient Education
- Review all regenerative options and provide guidance and rationale for your suggestion; guided by evidence and clinical experience
- Counsel: this process will take several months
- Great to consider this with an athlete or active person in season who does not want the "down time" for PRP/Stem cells and is willing to come in for more treatment over an extended period of time

ABSTRACT #2

Prolotherapy for Knee OA: An Evidenced-based Review

David Rabago, MD. University of Wisconsin, Madison, WI.

Objectives: are to introduce prolotherapy, provide brief biological rationale, and to review a recent RCT and long-term follow-up and review studies assessing prolotherapy for knee OA.

Conclusion is that prolotherapy for knee OA is supported by rigorous clinical trial data and should be first line therapyin regenerative medicine.

Healthy Aging Research (2018) 7:e14
Published online 22 December 2017
http://dx.doi.org/10.1097/HXR.0000000000000014

ABSTRACT #3

Customized PRP Treatments to Manipulate Healing Mechanisms

Isabel Andia, PhD. Biocruces Health Research Institute, Cruces University Hospital, Spain.

Tendinopathies and joint conditions are unmet medical needs. The FDA defines unmet medical need as a condition whose treatment is not correctly addressed by available therapies. Is there any opportunity in PRP interventions?

PRP therapies emerged two decades ago as an attractive treatment approach to enhance tissue repair and regeneration. It's applied across specialties and pathologies with strong disparities. It would seem that we are painting everything with the same brush… there is no relationship between diagnostic and treatment.

In part for that reason, the efficacy is **controversial**. Moreover, within the same pathology, some patients are satisfied because they experiment significant pain reduction and important improvements in function; these patients are **responders** as they show very positive effects. Instead, other patients do not show improvements in outcomes; these patients are **non-responders**. These limitations in PRP efficacy give us the opportunity to explore novel ways for improving our treatments.

The rationale of PRP treatment, mechanism of action

First mechanism: platelet degranulation to provide supra-physiological concentrations of growth factors and cytokines at the injured/pathological tissues mimicking initial stages of healing.

Second mechanism (less explored): Direct interaction of platelets with cells.

How to improve the clinical response to PRP

The clinical effect after PRP administration is consequence of 1) **the quality of PRP** and 2) **the status of the recipient tissue** (i.e. reactive vs. degenerative).

1) The quality of PRP: quality can be affected by endogenous factors including age (example: parabiotic experiment in rats, old and young rats sharing a common blood supply); metabolic diseases (clinical example: diabetic patient, PRP in DFU; *in vitro* example: hyperuricemia and tenocytes); microbiota (example: rat study in tendon).

Injury: Importantly, systemic factors can be activated in response to acute injury, i.e. HGFA is an injury-regulated systemic factor that induces the transition of stem cells into G*Alert*.

Allogeneic PRP from qualified donors, why not? As a next step further.

2) **The status of the recipient tissue** (i.e. reactive vs. degenerative in tendons)

How to overcome deficiencies of the recipient tissue

Choose a plasma formulation depending on the effects you want to trigger:
- L-PRP to activate inflammatory mechanisms in degenerative tendons;
- L-PRP releasate to better stimulate angiogenesis.
- Pure PRP or PPP to stimulate tissue anabolism.

Use combinatory treatments, PRP + HA; PRP + exercise

PRP + cells: for example [PRP + SVF] in joint conditions, [PRP + dermal fibroblasts] in tendons

Co-administration of anesthetics and corticosteroids.

Take home message
- Limitations in PRP therapies give us the opportunity to explore novel ways for improving these therapies
- Endogenous (demography, comorbidities) and exogenous (medications) factors are potential modifiers of PRP actions
- PRP can be customized to specific conditions by selecting the most appropriate formulation and timing for application and/or by combining PRP with synergistic complementary treatments

New challenges involve biomarker development (informing about the state of the recipient tissue) and potency assays for PRP (inadequate understanding of PRP mechanisms hinders the development of potency assays)

ABSTRACT #4

Biologic Vitality

Allan Mishra, MD. Menlo Clinic, Menlo Park, CA.

This lecture focuses on the idea of blood as biologic vitality. We measure it to distinguish between sickness and wellness. We use fractions of blood and bone marrow to treat injuries and disorders. We must avoid exaggerated claims about biologic capabilities. In this talk, we dive into key questions such as: What components of blood are valuable? Are white blood cells good or bad? What would be an ideal formulation of PRP? And finally: can a device be designed to produce this pinnacle PRP formulation?

ABSTRACT #5

PRP Intraarticular and Intraosseous Infiltrations to Treat Osteochondral Lesions and Severe Osteoarthritis of the Knee

Mikel Sanchez, MD. Hospital Vithas San Jose, Vitoria, Spain.

This lecture covers PRP and degenerative joint pathology, including why, when, and how to use growth factors in joint pathologies. It examines PRP and OA clinical studies that combine intra-articular and intraosseous injections of PRP for Knee OA and looks at the standardization of PRP terminology as well as quality and quantity of existing PRPs.

ABSTRACT #6

A Comparison of the Use of PRP versus Hypertonic Glucose in SIJ Incompetence

J. Saunders. Sports Physician, University of Notre Dame, Sydney, AU.

PRP (RegenBCT) is a valid treatment for treating physical therapy resistant mechanical SacroIliac Joint incompetence.

- It works well with fewer injections required than hypertonic glucose.
- Long term results yield excellent recovery of normal function, decrease in pain and resumption of normal life.

ABSTRACT #7

Intradiscal Biologics: Where are we Going?

Gregory Lutz, MD. Regenerative SportsCare Institute, New York, NY.

Can We Apply What We Have Learned from our Regenerative Sports Practice Treating Tendon/Ligament Injuries To Patients with Spinal Disorders?

ABSTRACT #8

Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2M) Concentrate Alleviates Back Pain in FAC-Positive Patients

Gaetano J. Scuderi, MD. Orthopedic and Spine Surgeon, Jupiter, FL.

The purpose of this presentation is to determine the ability of FAC to predict response to biologic therapy with concentrated autologous A2M (Alpha-2-Macroglobulin) for patients with LBP from DDD.

ABSTRACT #9

A Neurosurgeon's Perspective on Regenerative Medicine

Daniel T. Laich, DO. Chicago Brain & Spine Institute, Chicago, IL.

Topics: Highlight neurosurgical uses already undergoing study

- Spinal Adaptations
- Develop a cogent treatment algorithm for diagnosis and appropriate treatment uses
- Understand importance of uniformity in treatment
- Registry data collection, studies

ABSTRACT #10

An Initial Orthobiologic Ethics Statement

Don Buford, MD. Dallas PRP & Stem Cell Institute, Dallas, TX.

Along with Drs. Chris Centeno and Steven Sampson, Dr. Don Buford breaks ground with an initial orthobiologic ethics statement for a rapidly expanding field. He includes calls for public data, regulation, and clear product descriptions.

ABSTRACT #11

Bringing Regenerative Medicine into the 21st Century with Advanced Manufacturing

James J. Yoo, MD, PhD. Wake Forest Institute for Regenerative Medicine Winston-Salem, North Carolina.

- Bioprinting technology is able to generate clinically relevant sized 3-D tissue constructs with precision
- Various technological obstacles/challenges must be addressed in order to build composite and complex tissues and organs
- Bioprinting technology may be an excellent tool that could accelerated translation into the clinic and change the way medicine is practiced

ABSTRACT #12

Rules of Engagement: FDA Regulation of Orthobiologics

Andrew S. Ittleman, Esq. Fuerst Ittleman David & Joseph, PL, Miami, FL.

Dr. Ittleman's lecture covers crucial parts of FDA regulation surrounding orthobiologics, touching on these main areas:

- Same Surgical Procedure Draft Guidance
- Minimal Manipulation Draft Guidance
- Adipose Tissue Draft Guidance
- Homologous Use Draft Guidance
- FDA Public Hearing on all Draft Guidances
- Medical Device Draft Guidance (21st Century Cures Act, § 3034)
- RAT Standards Required
- Regulations and Guidance to be updated

ABSTRACT #13

"Synapse-like" Connections between Adipose Tissue MUSE Stem Cells and Adipocytes: Morphological and Molecular Features of Human Adipose.

Cristina Bertolotto, MD. ClusterXStem Inc, Los Angeles, CA.

Adipose tissue (AT) isolated by human liposuction is derived from the embryonic mesenchyme and contains a complex mixture of cells composed of adipocytes, a stroma vascular fraction, and two types of adult adipose stem cells: adipose mesenchymal stem cells and multi-lineage differentiating stress enduring cells (MUSE Stem cells). Both adipose mesenchymal-derived stem cells and AT derived pluripotent stem cells have potential applications for the repair and regeneration of tissues that are acutely or chronically damaged. However, numerous aspects of biological characteristics of human AT derived pluripotent stem cells have yet to be elucidated. Our study provides insight into unique morphological and molecular characteristics of these cells. In this study, human adipose tissue recently extracted, minced, and centrifuged for 10 minutes. We performed immunostaining to explore the role of stem cell markers, and electron microscopy (EM) techniques. EM analysis found that the small cells have an intimate relationship, which we refer to here as "Synapseslike", with both adipocyte progenitors and adipocytes. Our data demonstrates that AT derived pluripotent stem cells constitute a homogeneous cell population (in both, morphology and size) that needs to be in direct "Synapse-like" communication with more differentiated cells. This type of direct cell-to-cell communication, much like a traditional synapse, may be vital to cell development, and may play a role in cell dormancy, or activation upon induction of stress and alteration of the "synapse-like" communication. We observe that each type of cell has a unique molecular profile, which could allow

the adipose tissue derived pluripotent stem cells to be resistant to severe cellular stress conditions, which is a key characteristic of the MUSE stem cell. Additional pre-clinical, clinical safety and efficacy studies are necessary to demonstrate the important value of the MUSE stem cells may hold for regenerative medicine and cell therapy.

ABSTRACT #14

MSCs: The State of Science. MSCs are Not Stem Cells

Arnold I. Caplan, PhD. Case Western Reserve University, Cleveland, OH.

Slides & video lecture online & Flash Drive, no abstract

ABSTRACT #15

It Takes Two to Tango: MSCs and Biomimetric Scaffolds

Rocky S. Tuan, PhD, MD. University of Pittsburgh, Pittsburgh, PA.

This lecture reviews topics such as reconstructing soft tissues, autograft/allograft limitations, commonly used tissue decellulaization protocol, decellularized tissues as grafts, tendon tissue engineering, cartilage tissue engineering, region-specific meniscal ECM, meniscus tissue engineering, and more.

ABSTRACT #16

BMC Treatment for Knee Osteoarthritis: 2 Year Prospective Trial and Cellular Analysis of Single versus Multiple Site Marrow Harvesting Techniques

Kristin Oliver, MD. Bluetail Medical Group, Chesterfield, MD.

The lecture will present Bluetail Medical Group's ongoing Case Series data for patients with knee osteoarthritis who have undergone a percutaneous Bone Marrow Concentrate Graft. It will also present data from a recently published case series comparing differing bone marrow aspiration techniques.

ABSTRACT #17

Perc-ACLR

Christopher Centeno, MD. Centeno-Schultz Clinic, Broomfield, CO.

Between 1994 and 2006, ACL reconstructions increased by 37% to 134, 421 total procedures. Dr. Centeno presents & examines three key questions we should ask in regards to ACLR:

1. Will reconstructing the ACL prevent arthritis?
2. Will the surgery help the patient get back to sports quicker?
3. Will the knee ever be the same post surgery?

ABSTRACT #18

Quantitative Analysis of BMC and PRP Samples: Experience in a Clinical Setting

David Karli, MD, MBA. Steadman Clinic, Vail CO.

Physicians using PRP and BMC as an autologous, regenerative therapy to treat a variety of orthopedic pathologies has exploded in recent years. The preparations are FDA-compliant if used at point-of-care during the same surgical procedure. However, the levels of various critical components of these orthobiologic preparations are rarely determined or quantified. In contrast, PRP and BMC samples used at The Steadman Clinic have a 27-parameter sample analysis performed on both the source material and the resulting PRP and BMC preparations. Of critical interest are the level of platelets, RBCs and the differential CBC results that are provided to the physician prior to treatment. Trends from the component analysis for PRP and BMC samples produced at The Steadman Clinic over the past 2 years will be reviewed, including residual levels of granulocytes and RBCs present in depleted PRP preparations.

ABSTRACT #19

Treating Pain from the Subchondral Bone

Jason L. Dragoo, MD. Stanford University, Stanford, CA.

In this examination of treating pain from the subchondral bone, types of bone marrow lesions are examined, as well as evidences that bone marrow lesions cause pain. Cartilage defects involving subchondral bone are also examined as Dr. Dragoo discusses biologic treatments for bone marrow lesions.

Summary

- Pain can be experienced from a cartilage defect but also from the subchondral bone
- Lesions can be treated using different approaches:
  - Biologic
  - Structural
- More comprehensive treatment of pain generators will likely lead to improved results

ABSTRACT #20

Injection of Autologous Micro-fractured Non-expanded Adipose Tissue: General Database Results and Knee Meniscus Tear Study

Jay E. Bowen, DO. New Jersey Regenerative Institute, Cedar Knolls, NJ.

The lecture will briefly review SVF for orthopedic issues focusing on the hip and knee. It will provide comments on adipose and SVF composition. Dr. Bowen will be reviewing data from NJ Regenerative Institute's database on an adipose treatment for orthopedic conditions and review preliminary data on a prospective IRB approved degenerative meniscal tear study. He will also provide additional database results regarding treatment for knee osteoarthrosis groups.

ABSTRACT #21

A Randomized Clinical Trial of Allogeneic Adipose Stem Cells in Canine Osteoarthritis

Robert Harman, DVM. VetStem, Poway CA.

Osteoarthritis (OA) is a degenerative joint disease with a high prevalence in dogs. Mesenchymal stem cells have been used to treat humans, dogs, and horses with OA. This presentation describes a prospective, randomized, blinded, and placebo-controlled clinical efficacy study of intraarticular allogeneic adipose stem cells for the treatment of dogs with osteoarthritis. Health assessments and measurements of pain and activity impairment were performed at baseline and at selected time points through day 60. The primary outcome variable was the owner Client-Specific Outcome Measurement (CSOM) and secondary measures included veterinary pain on manipulation, veterinary global score, and owner global score. The dogs were treated with either a saline placebo or a single dose of allogeneic adipose-derived mesenchymal stem cells in either one or two joints. Seventy-four dogs were statistically analyzed for efficacy outcomes. Success in the primary outcome variable, CSOM, was statistically improved in the treated dogs compared to the placebo dogs (79.2% vs. 55.4%, $P = 0.029$). The veterinary pain on manipulation score (92.8% vs. 50.2%, $P = 0.017$) and the veterinary global score (86.9% vs. 30.8%, $P = 0.009$) were both statistically improved in treated dogs compared to placebo. There was no detected significant difference between treated and placebo dogs in the incidence of adverse events or negative health findings. Allogeneic adipose-derived stem cell treatment was shown to be efficacious compared to placebo. This large study of dogs also provides valuable animal clinical safety and efficacy outcome data to our colleagues developing human stem cell therapy.

ABSTRACT #22

The Use of Adipose Derived Progenitor Cells and Platelet Rich Plasma Combination for the Treatment of Supraspinatus Tendinopathy in 55 Dogs: A Retrospective Study

Sherman O. Canapp Jr, DVM, MS, DACVS. Veterinary Orthopedic and Sports Medicine, Annapolis Junction, MD.

Objective: To report clinical findings and outcomes for 55 dogs with supraspinatus tendinopathy treated with adipose derived progenitor cells and platelet rich plasma therapy.
Methods: Medical records of client-owned dogs diagnosed with supraspinatus tendinopathy that were treated with adipose derived progenitor cells and platelet rich plasma (ADPC-PRP) combination therapy were reviewed from 2006-2013. Data collected included signalment, medical history, limb involvement, prior treatments, physical and orthopedic examination, objective temporospatial gait analysis findings, diagnostic imaging results (radiography, magnetic resonance imaging, musculoskeletal ultrasonography), arthroscopy findings, and outcome.
Results: Following ultrasound-guided injection of ADPC-PRP, objective gait analysis was available on 25 of the 55 dogs at 90 days post ADPC-PRP therapy. Following treatment, a significant increase in total pressure index percentage (TPI%) was noted in the injured (treated) forelimb at 90 days post treatment ($P = 0.036$). At 90 days following treatment, 88% of cases had no significant difference in TPI% of the injured limb to the contralateral limb. The remaining 12% of cases had significantly improved ($P = 0.036$). Bilateral shoulder diagnostic musculoskeletal ultrasound revealed a significant reduction in tendon size (CSA) in the treated tendon at 90 days following treatment when compared to the initial CSA ($P = 0.005$). All cases showed significant improvement in fiber pattern of the affected supraspinatus tendon by the ultrasound shoulder pathology rating scale.
Clinical Relevance: These findings suggest that ADPC-PRP therapy should be considered for dogs with supraspinatus tendinopathy.
Abbreviations: ST: supraspinatus tendinopathy ADPC: adipose derived progenitor cells MSC: mesenchymal stem cells PRP: platelet rich plasma TPI%: total pressure index percentage

ABSTRACT #23

Combination of PRP and Adipose Stem Cells: Scientific and Clinical Rationale

Randy Miller, MD. Miller Plastic Surgery, Miami, FL.

This lecture will focus on the scientific basis and clinical experience that has led to the frequent utilization of adipose stem cells in combination with platelet rich plasma (PRP) for musculoskeletal disorders. In addition to basic science, the lecture will contain information regarding the treatment protocol and ratio of combined biologics at the point of care. To validate the scientific and clinical rationale for this combined biologic therapy, we will embark on a prospective double-blind randomized placebo-controlled study using minimally manipulated adipose tissue combined with platelet rich plasma for the treatment of mild osteoarthritis of the knee. The study is currently being designed and will include the treatment and follow-up of 100 patients.

ABSTRACT #24

New Biologic Approaches to Save the ACL

Ignacio Dallo, MD. Sanatorio Garay Hospital Santa Fe, Argentina.

Introduction: Anterior cruciate ligament reconstruction (ACLR) has been established as the gold standard for treatment of complete ruptures of the anterior cruciate ligament (ACL) in active, symptomatic individuals. In contrast, treatment of partial tears of the ACL remains controversial. Biologically augmented ACL-repair techniques are expanding in an attempt to regenerate and improve healing and outcomes of both the native ACL and the reconstructed graft tissue.
Hypothesis/Purpose: The purpose of this paper was to review the biologic treatment options for partial tears of the ACL.
Study Design: Current Concept Review
Methods: A literature review was performed that included searches of Pubmed, Medline, and Cochrane databases using the following keywords: Partial Tear of the ACL, ACL Repair, Bone Marrow Concentrate, Growth factors/Healing enhancement, Platelet Rich Plasma, Stem Cell Therapy.
Results: The use of novel biologic ACL repair techniques, including growth factors, PRP, stem cells and bio-scaffolds, have been reported to result in promising pre-clinical and short-term clinical outcomes.
Conclusion: The potential benefits of these biological augmentation approaches for partial ACL tears are improved healing, better proprioception and a faster return to sport and activities of daily living when compared to standard reconstruction procedures. However, long term studies with larger cohorts of patients and techniques validation are necessary to assess the real effect of these approaches.

ABSTRACT #25

Platelet Rich Plasma (PRP) versus Bone Marrow Concentrate (BMC) in Treating Tendonopathy

Alan Hirahara, MD, FRCS. Sacramento Orthopedic Center, Sacramento, CA.

Tendinopathy refers to a disease of a tendon. This comprises inflammation to partial tear to full tear. In general, we discuss the treatment of inflamed tendons to partial tears using platelet rich plasma, mesenchymal stem cells, and adipose tissue. Stem cell and adipose usage has increased recently with the ability to diminish white cells, which are detrimental to healing. More data is emerging showing PRP is useful in tendinopathy. However, there do seem to be limits about how much damage can be addressed with PRP alone. With the use of stem cells, we are seeing better outcomes with larger tendon lesions than we could previously treat with PRP alone. Fat is also emerging as another option for these injections that may be easier and safer to harvest.

ABSTRACT #26

Biologic Knee Reconstruction: Meniscus Allograft and Articular Cartilage Paste Grafting for Athletes and Arthritis. A Role for Amnionic Stem Cells?

Kevin R. Stone, MD. The Stone Clinic, San Francisco, CA.

Slides & video lecture online & flash drive, no abstract

ABSTRACT #27

Intraneural and Perineural Infiltrations of PRGF in Peripheral Nerve Injuries

Sabino Padilla, MD, PhD. Biotechnology Institute, Vitoria, Spain.

Dr. Padilla reviews four main areas in this presentation on peripheralnerve injuries:

1. Biology of nerve regeneration
2. PRPs: Gathering evidence and plausible mechanisms
3. PRP intervention and applications on neuropathies
4. PRP intervention to improve Lower Back Pain

After a thorough review of basic science behind all four topics, Padilla concludes that fluoroscopy-guided infiltrations of intervertebral discs and facet joints with plasma rich in growth factors in patients with chronic low back pain resulted in significant pain reduction assessed by VAS.

ABSTRACT #28

ESWT for Tendinopathy

Nicola Maffulli, MD, MS, PhD. Queen Mary University of London, England.

Slides & video lecture online & flash drive, no abstract

ABSTRACT #29

Orthobiologics for Musculoskeletal Conditions: Sumary Protocols, Best Evidence, and Rationale

Dallas Kingsbury, MD. NYU Langone, New York, NY.

General Principles of the Orthobiologics Protocols Summary Presented:

- Most protocols pre-suppose other conservative measures have been tried
- Some recommendations are based on prospective trials or reviews, retrospective/ case studies, basic science, or expert opinion
- No particular vendors of orthobiologics products or preparatory equipment will be recommended
- Nothing replaces common sense and sound clinical-judgement
- Expectation management

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