Pre-clinical testing of a novel, injectable, tissue modifying device for the treatment of spinal disc degeneration and associated low back pain

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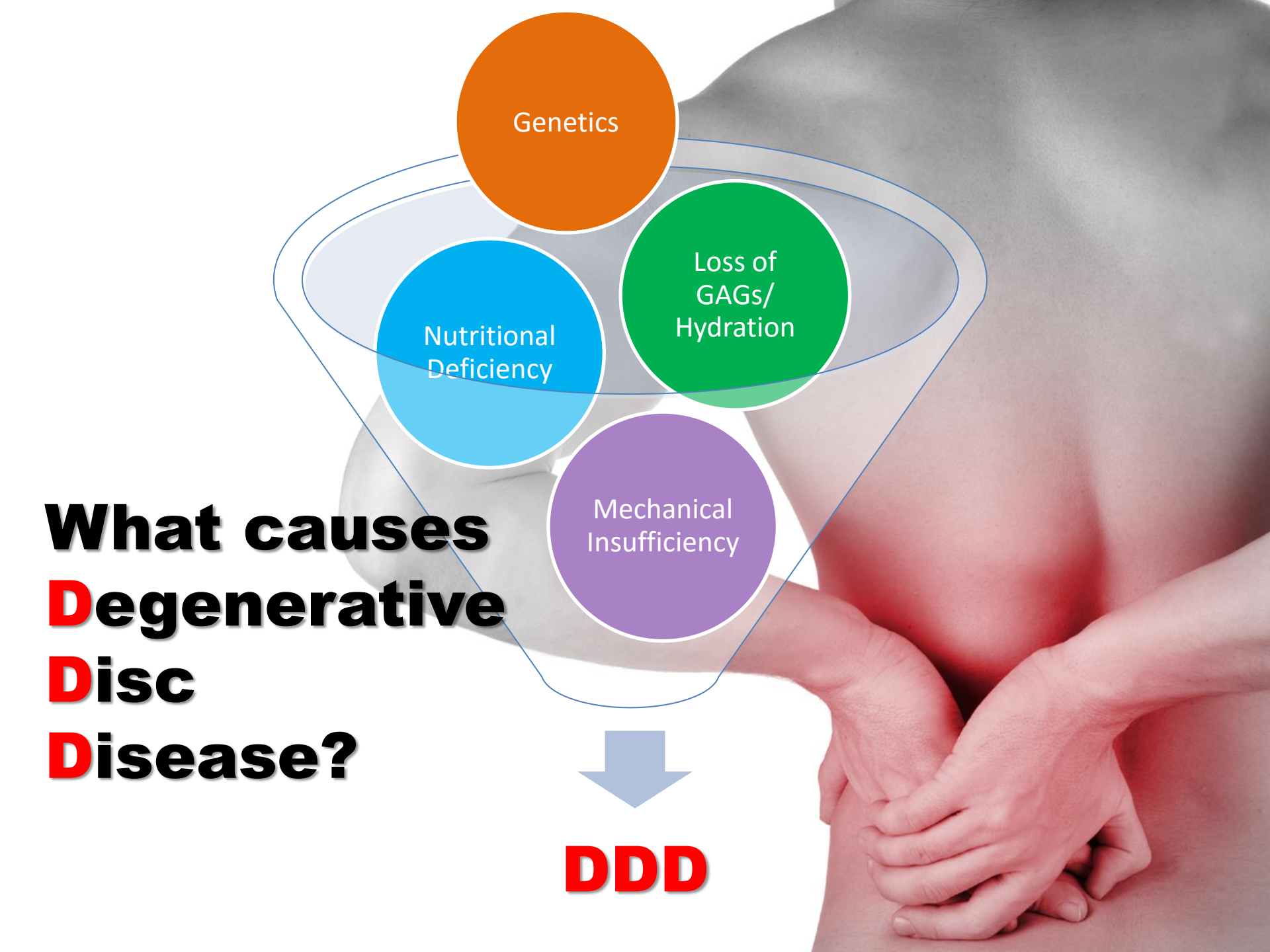
Degenerative Disc Disease (DDD) and Low Back Pain (LBP)

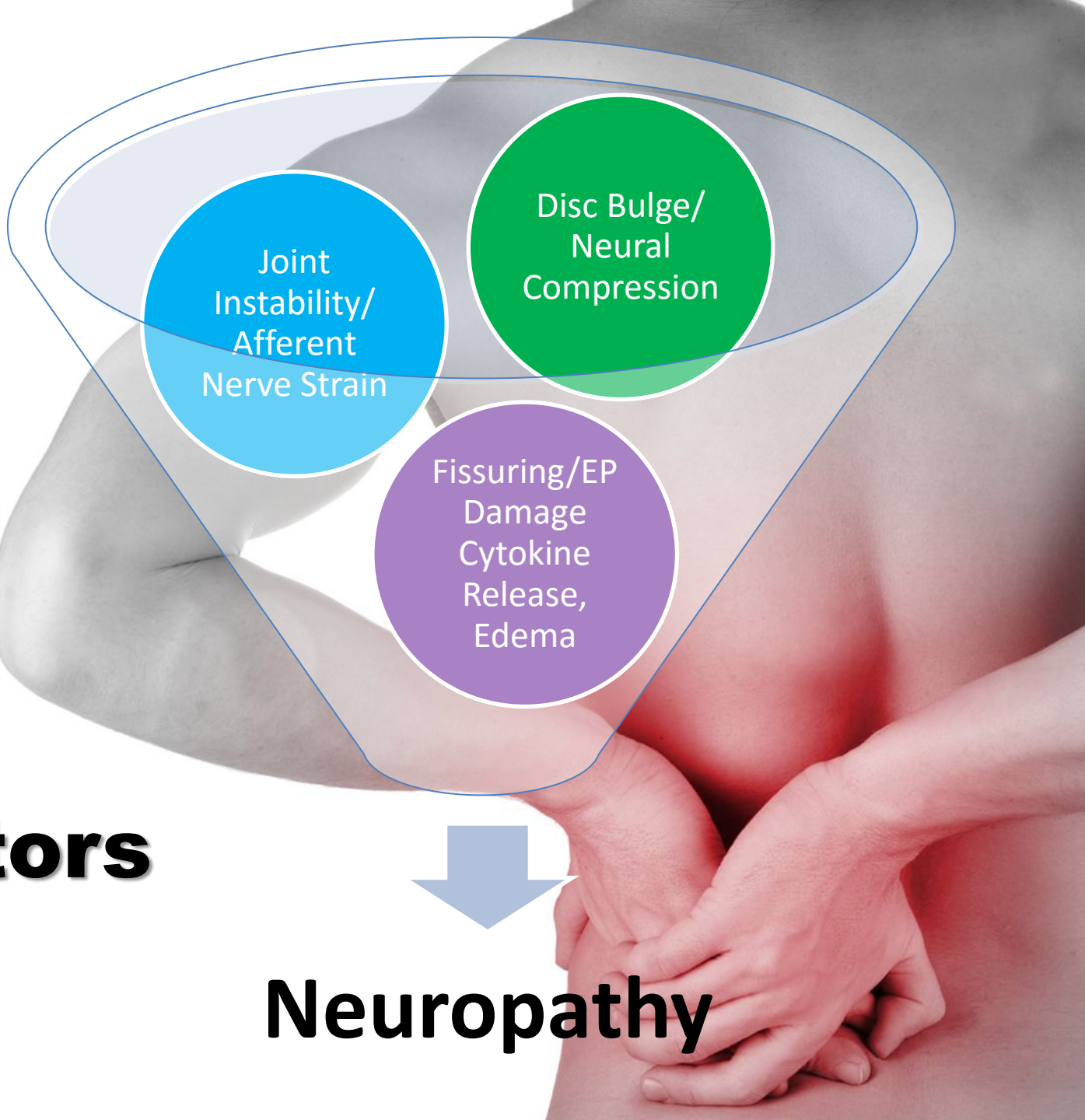
- **3rd most common reason for surgery**
- **In US (per year)[1]:**
  - 19 million office visits for LBP
  - 298,000 lumbar spinal fusions
  - 300,000 lumbar discectomies
- **LBP is usually associated with DDD but DDD is also common in asymptomatic patients[2-4]**
- **US economic cost of $100 billion[1]**

[1]Katz 2006, *JBJS* [2]Powell, 1986, *Lancet* [3]Buckwalter, 1995, *Spine* [4]Modic, 2007, *Radiology*


Genetics
Nutritional Deficiency
Loss of GAGs/ Hydration
Mechanical Insufficiency
What causes Degenerative Disc Disease?
DDD

Associated Biomarkers:

- Disc Bulge
- Joint Instability
- Fissures into outer 30% of AF
- AF HIZs (T2)
- Modic I&II adjacent to EP



Pain Generators

Neuropathy

Disc Therapeutic Performance Criteria

Underlying Factors - DDD

- ❑ Change Genetics?
- ❑ Increase nutritional flow/permeability/GAG retention?
- ❑ Improve mechanical properties/ durability?

Pain Generators

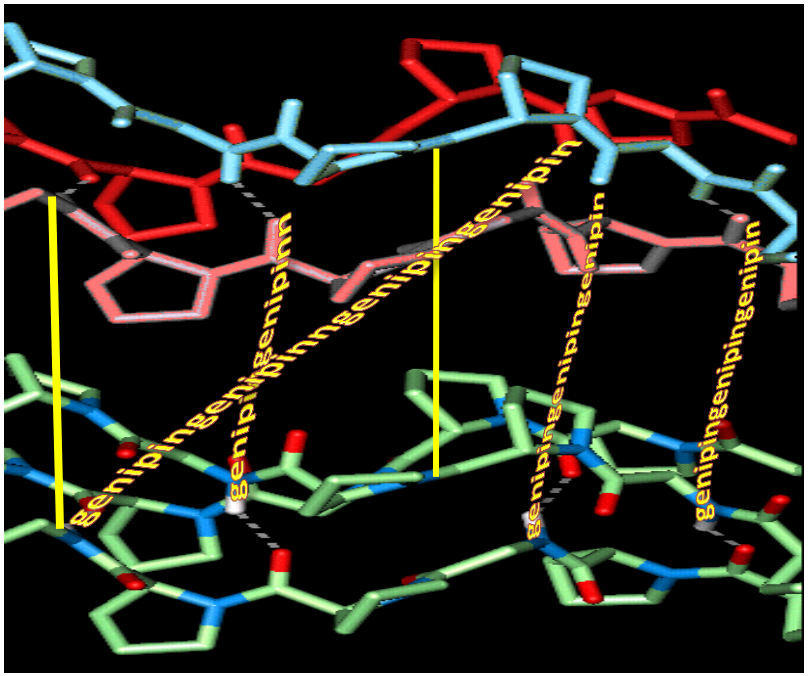
- ❑ Reduce disc bulge?
- ❑ Reduce joint instability?
- ❑ Increase tear resistance?
- ❑ Provide adhesion of adjacent tissues?

Other Criteria

- ❑ Ensure minimal toxicity?
- ❑ Useful as an adjunct to surgery?
- ❑ Fast-acting / Long-lasting?
- ❑ Inexpensive?

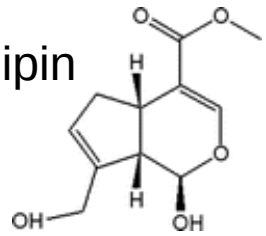
Injectable Matrix Modification

- **Crosslink augmentation of native tissue/ECM**
- **A non-biologic, biomimetic solution for avascular/ biologically challenged tissues**
- **Immediately effective/ long-lasting covalent bonds**
- **Inexpensive to produce**
- **“Flexible Fusion”**

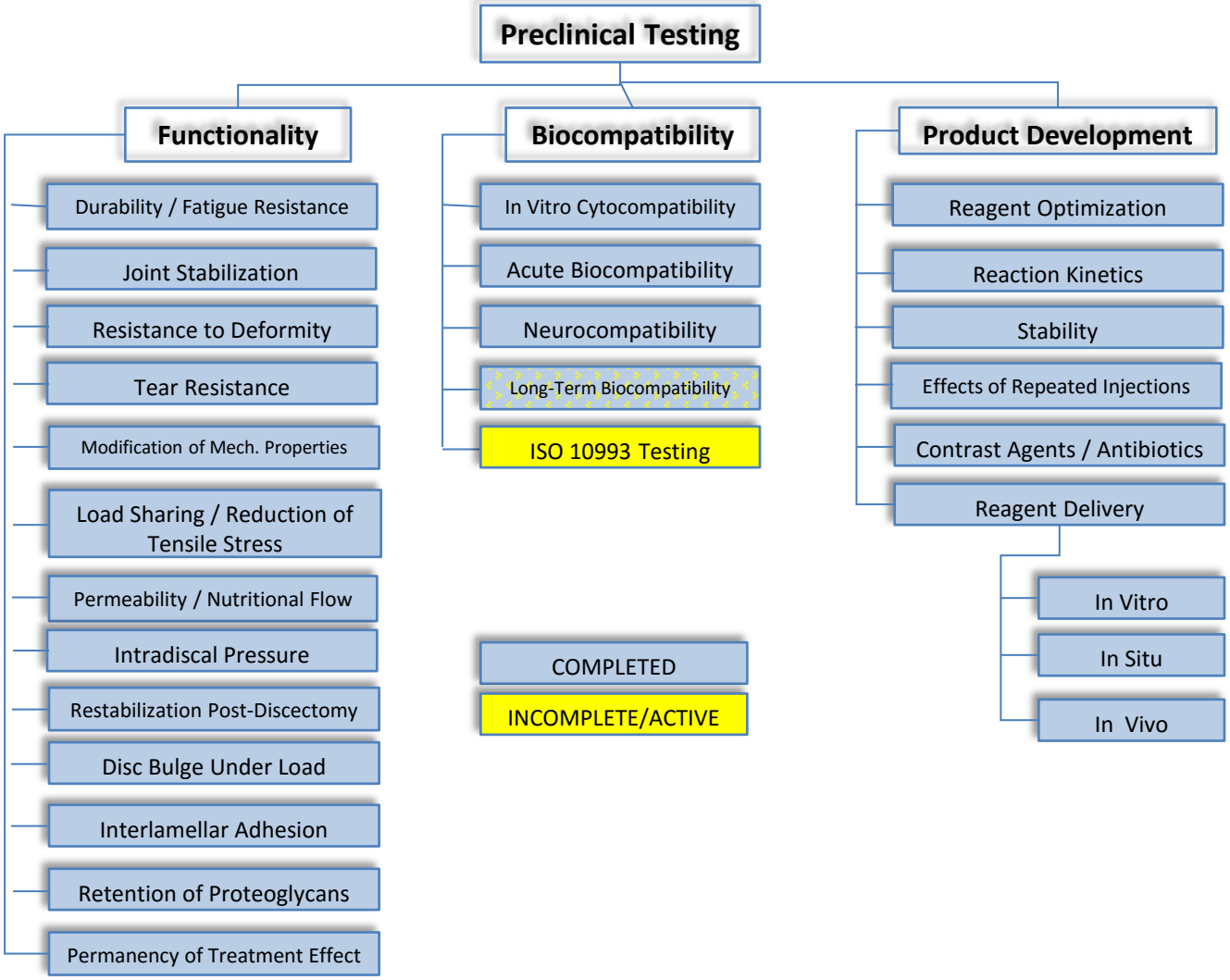


- **Injectable collagen crosslinking**
- **Immediate effect**
- **Long-lasting covalent bonds**

Genipin



Preclinical Studies Overview



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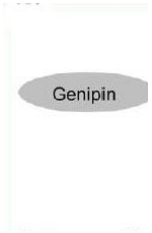
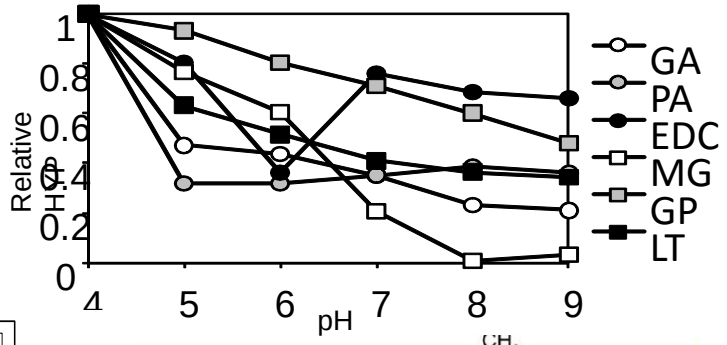
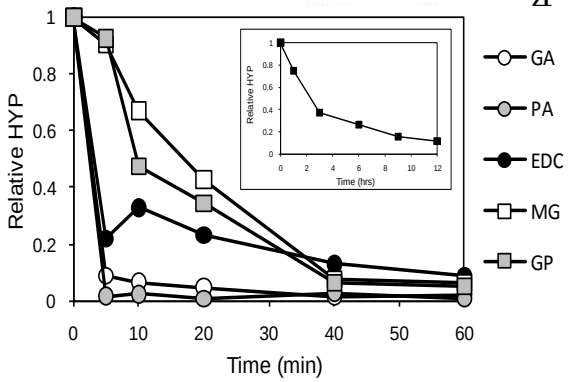
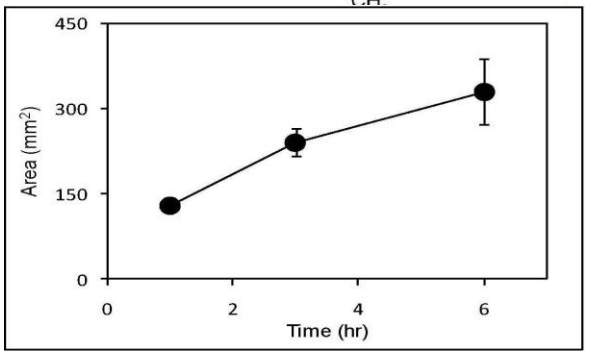
Biochemistry of Collagen Crosslinking

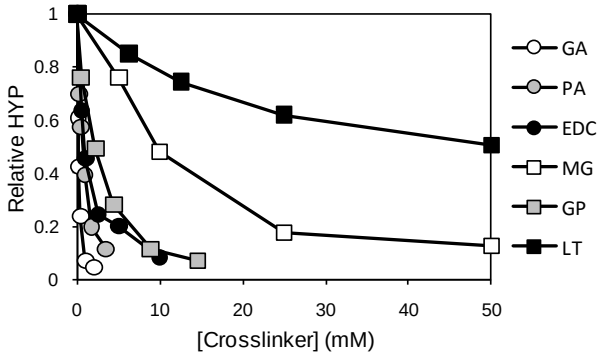
- Crosslinkers Evaluated – all react with primary (NH2) amine groups on amino terminal of polypeptide chain and on functional groups of lysine and argenine
  - Genipin
  - Methylglyoxal
  - EDC (amine to carboxy
  - L-Threose
  - Proanthrocyanidin
  - *Glutaraldehyde*
- Differences:
  - **Rate of reaction**
  - **Size of molecule/diffusivity**
  - pH optima (typically alkaline)
  - Length of resulting crosslink
  - **Ability to polymerize forming crosslinks of various lengths**





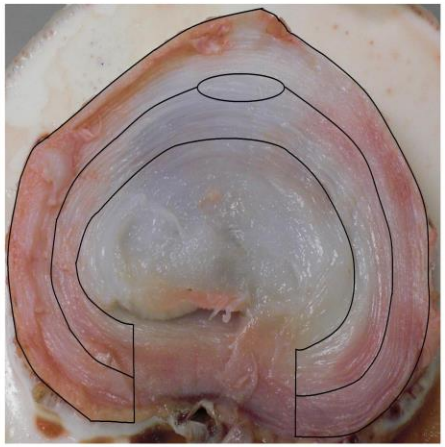


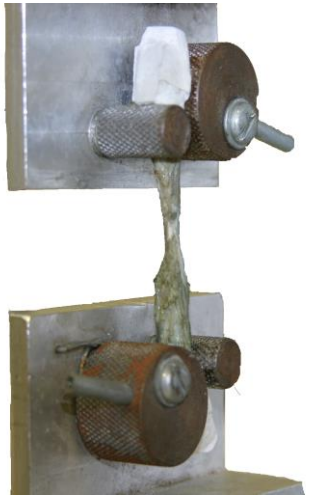




Research Aim: Does Genipin Crosslinking Improve Mechanical Properties & Durability?

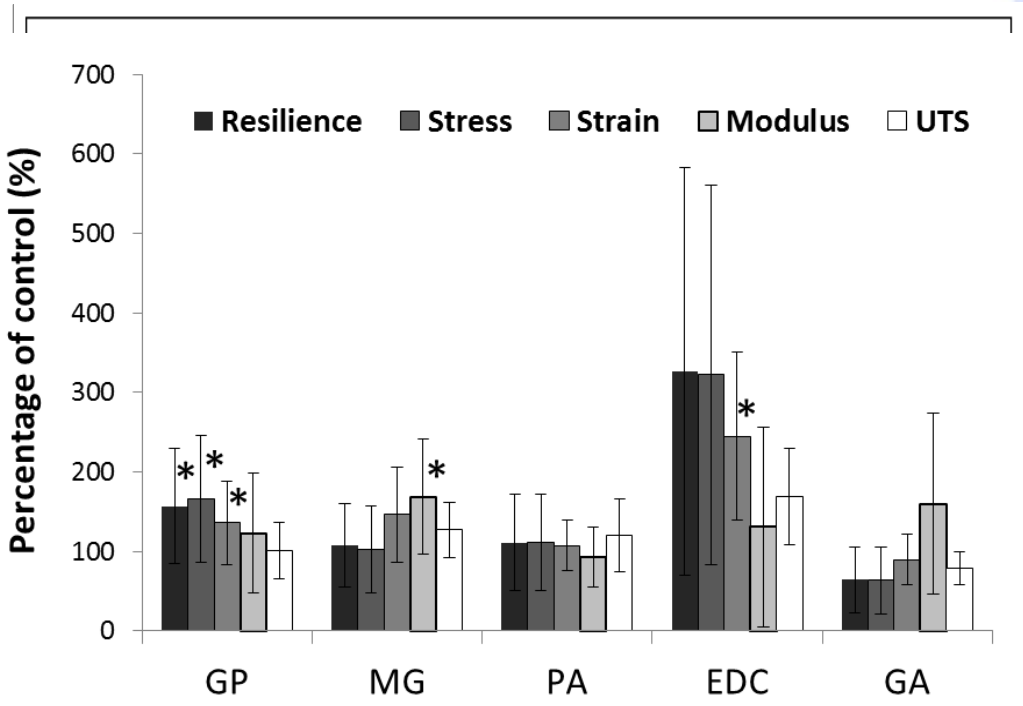
Experiments: In vitro compressive and tensile testing, and fatigue resistance testing of bovine discs.





Results: →

Underlying Factors

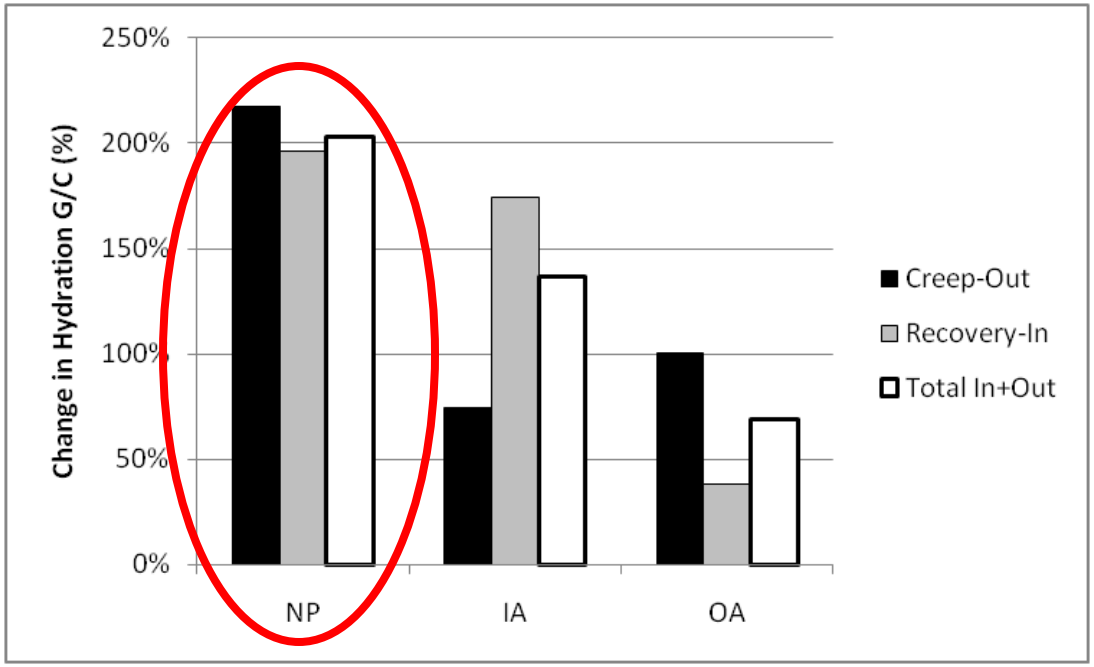


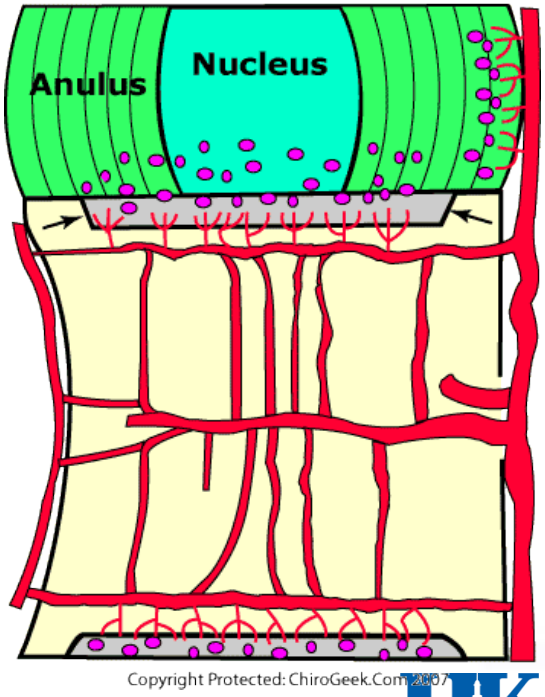
Research Aim: Does Genipin Crosslinking Increase Nutritional Flow/ Permeability?

Underlying Factors

Experiment: Hydration changes were measured following compressive loading and unloading

Results:





Implications: Double nutritional flow, improve diurnal irrigation

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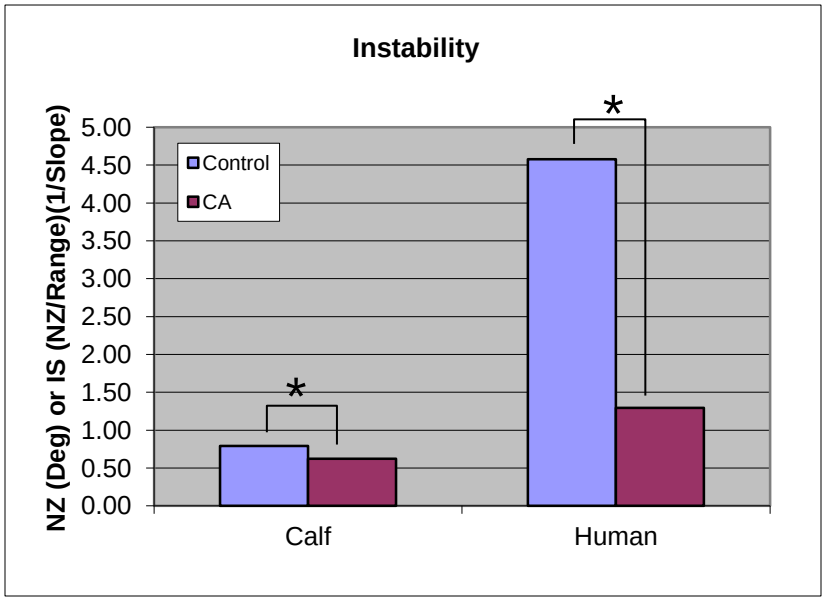
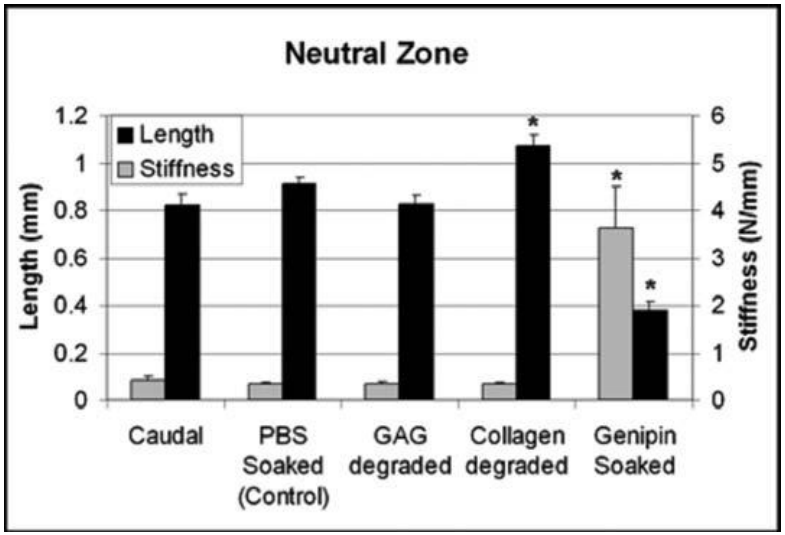
Research Aim: Does Genipin Crosslinking Reduce Joint Instability?

Experiment: Standard stability tests with soaked and injected human and bovine motion segments

Results:





Pain Generators

Implications: Joint instability has been linked to clinical incidence of pain, is thought to be associated with increased strain of imbedded afferent nerves.

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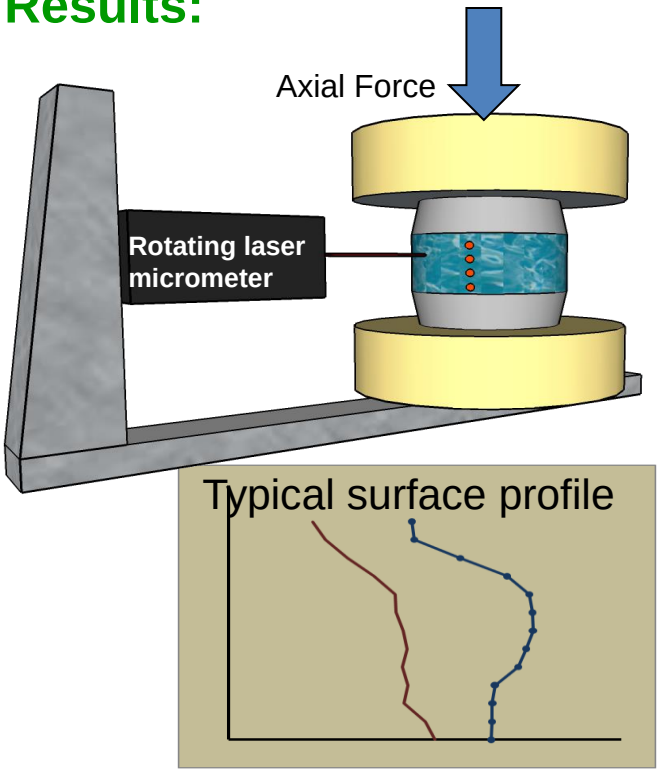
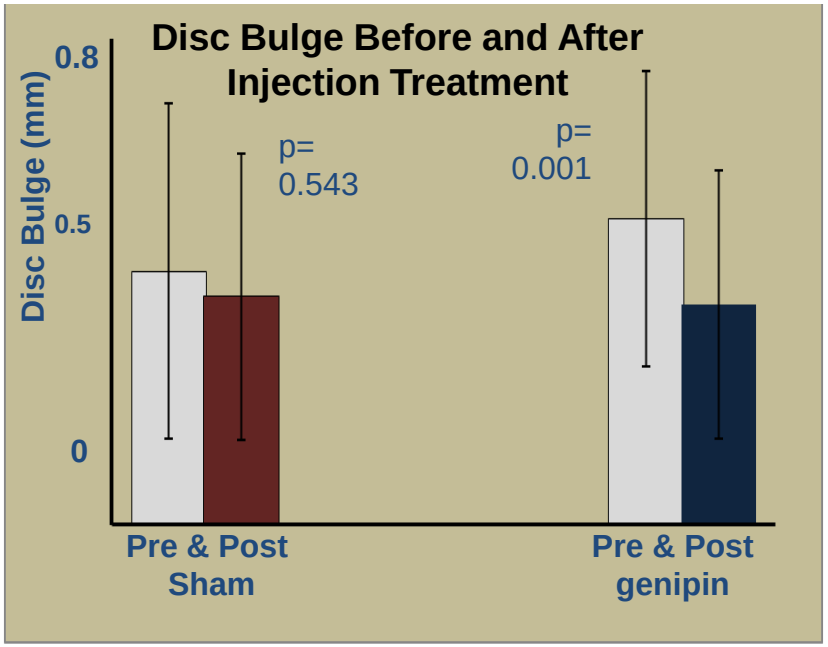
Research Aim: Does Genipin Crosslinking Reduce Disc Bulge

Experiment: Bovine lumbar discs loaded in compression and surface profile measured with laser system.

Results:





Pain Generators

Implications: >25% reduction in disc bulge under load, reduction comparable to strain threshold for afferent nerves

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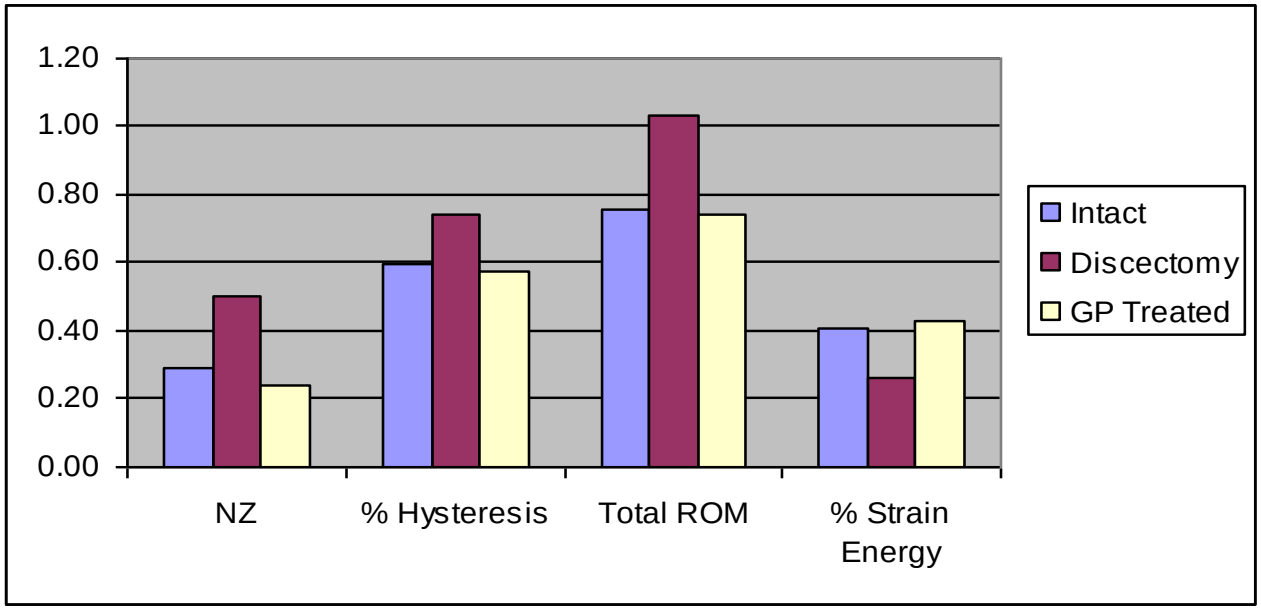
Research Aim: Is Genipin Crosslinking Useful for Restabilizing the Joint Post-Discectomy?

Results:



Other Criteria

Implications: Successfully addresses clinical need – restoration of mechanics following removal of load supporting tissues

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Large-Animal Long-Term Biocompatibility Study

Evaluate long-term (6 month) **safety/biocompatibility** of genipin reagent in IVD

Evaluate image-guided (fluoro) **delivery** of reagent to disc

Assess **effects** of treatment

4 young, healthy sheep

- Not a model of DDD pathology
- 2 treated lumbar discs per animal
- Phase 1 of 2 (8 sheep total)

Study conducted at Cincinnati Children's Hospital Medical Center (CCHMC)

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Large-Animal Long-Term Biocompatibility Study

16/16 successful fluoroscopic image-guided injections into 8 lumbar discs of 4 sheep

Up to 1 ml of GP-Buffer-Contrast solution injected per side into annulus fibrosis (AF)

- 50 mM GP
- 50mM (pH 9) EPPS/Phosphate

Presence of agent within annulus was confirmed with CT and fluoroscopy

Long term health monitoring

- Regular checkups by vet staff
- Food/water ingestion monitored
- Bloodwork done periodically (CBC, Chem-20)

MRI prior to euthanasia

- T1 and T2

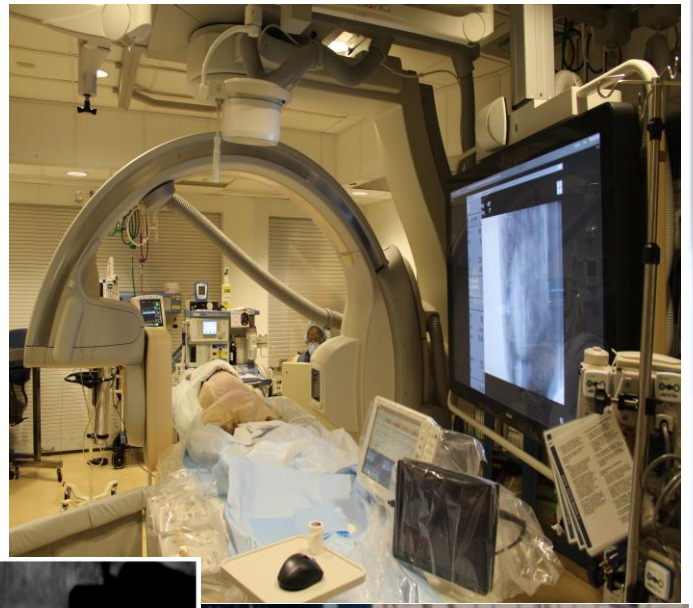
Mechanical testing of IVD

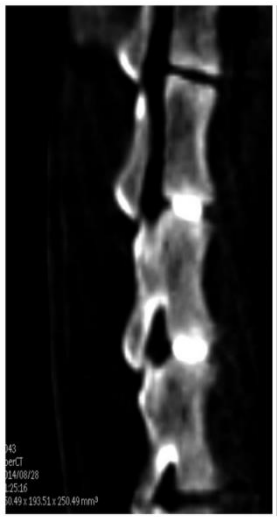
- Axial compression with bending
- 5 cycles
- Bending stiffness and hysteresis

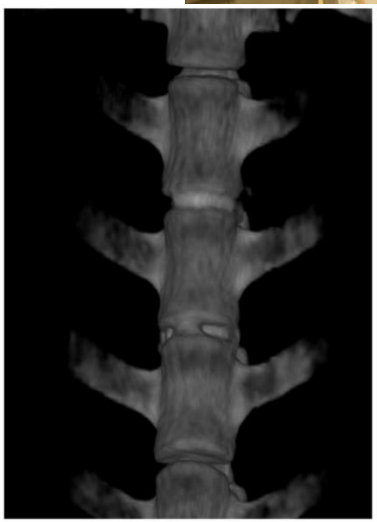
Histology

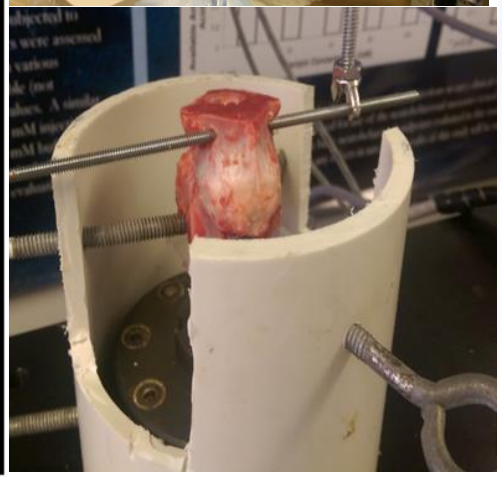
- H&E (IDEXX BioResearch)

Necropsy (as needed)

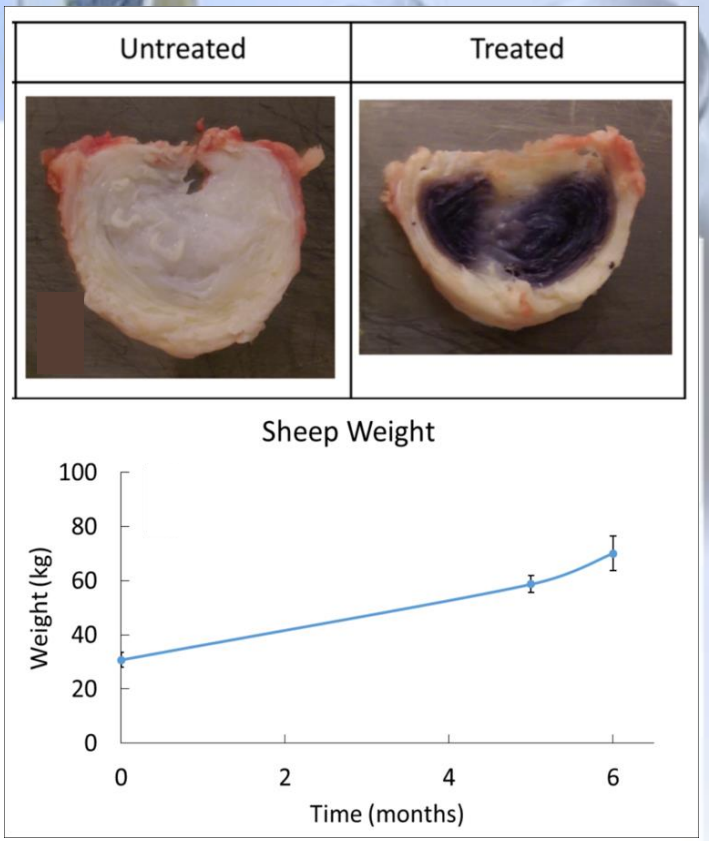








Large-Animal Long-Term Biocompatibility Study



Results: Primary Objectives

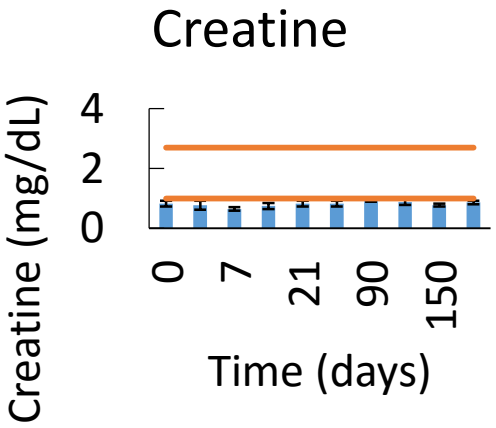
No observations of irregular sheep behavior or gait

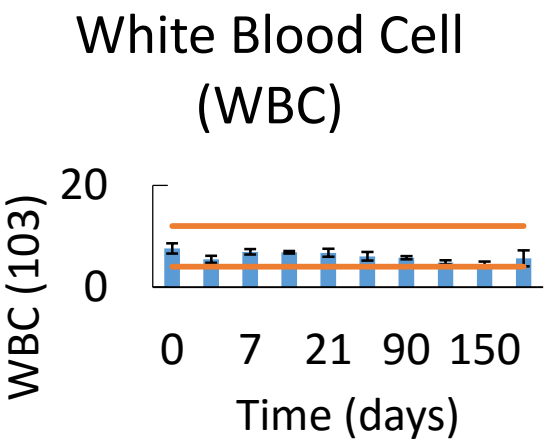
"Very happy sheep" within hours after procedure

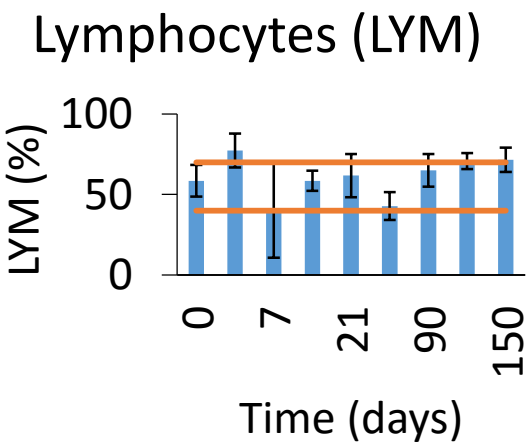
No concerning changes in body weight or temperature

Bloodwork was within normal levels

No inhibition of growth of adjacent tissues







Large-Animal Long-Term Biocompatibility Study

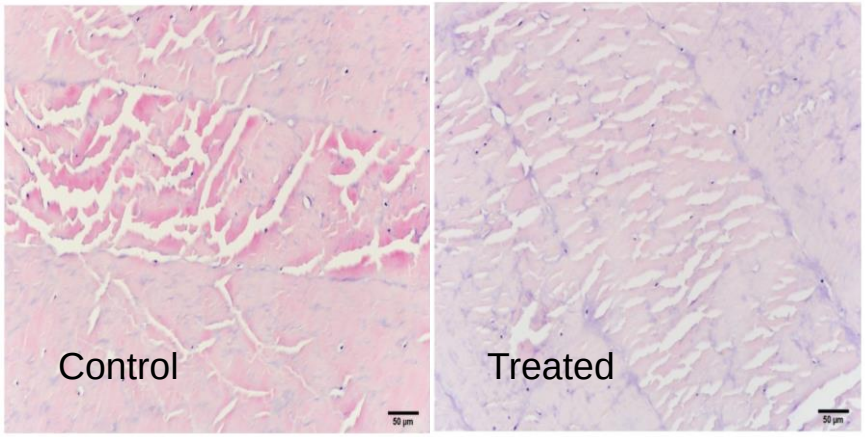
Results: Biomechanics

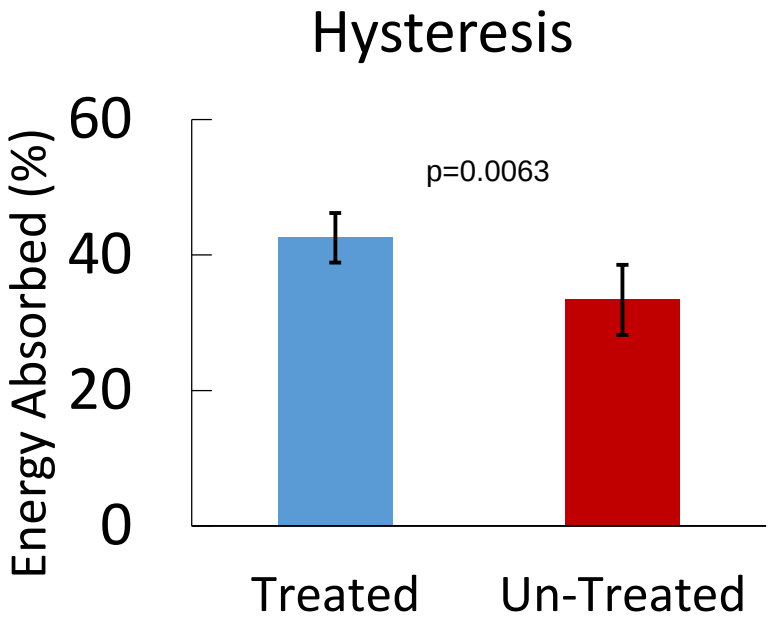
Joints treated with GP showed higher compression-bending stiffness which agrees with previous *in vitro* studies

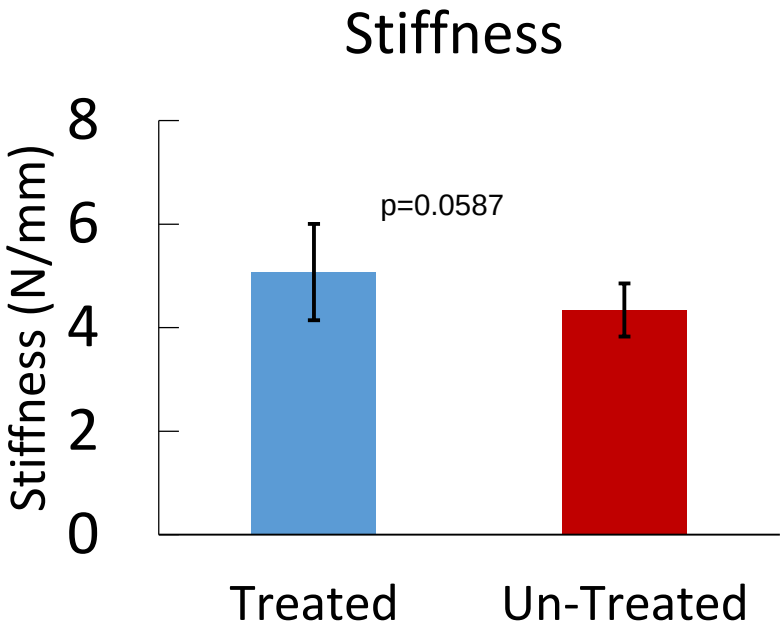
Mechanical effects moderated by new AF tissue

Results: Histology

No signs of infection, inflammatory response, or depletion of native cells from either the control discs or the treated discs







Performance as a Disc Therapeutic

Underlying Factors - DDD

- ✘ No effect on genetics
- ✓ Increases nutritional flow 100% / GAG retention 50%
- ✓ Improves mechanical properties/ durability 25%-300%

Pain Generators

- ✓ Reduces disc bulge >25%
- ✓ Reduces joint instability 4-fold
- ✓ Increases tear resistance >50%
- ✓ Provides adhesion of adjacent tissues >50%

Other Criteria

- ✓ Exhibits minimal toxicity (sub-cu; neurotox; large-animal, 6-month study; total of 9 studies)
- ✓ Fast-acting / Long-lasting / Inexpensive
- ✓ Repeatable (2X@40mM ≈ 1X@80mM)
- ✓ Useful as an adjunct to surgery (discectomy, adjacent disc)

Current Research Focus

Clinical trials approved in Malaysia

- Planned expansion into Canada and US

To treat lower back pain in patients 20-60 years old with DDD

Aims of studies for CE approval:

- 35-40 patients
- No serious adverse events
- Reduction of pain and disability at 1 and 3 months
- Followed for 6 months

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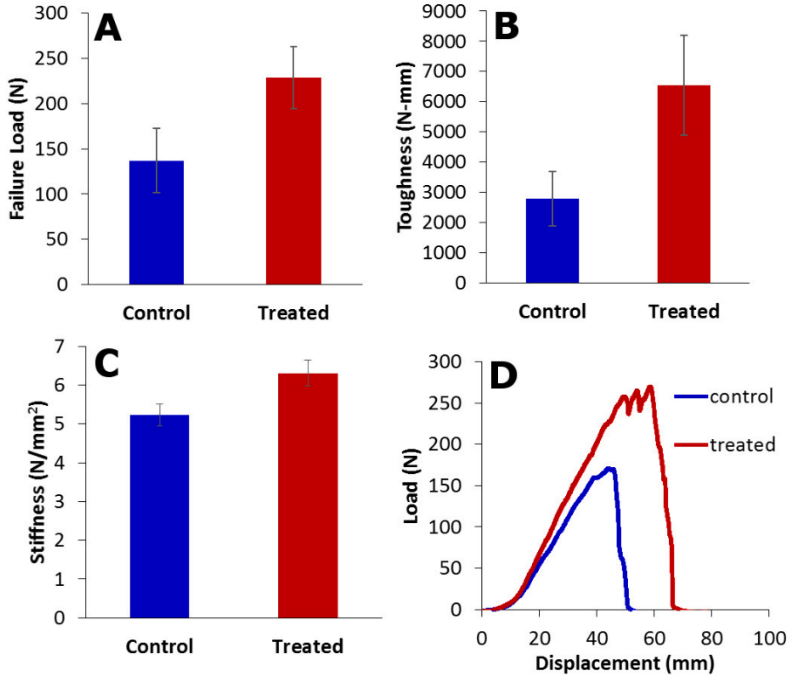
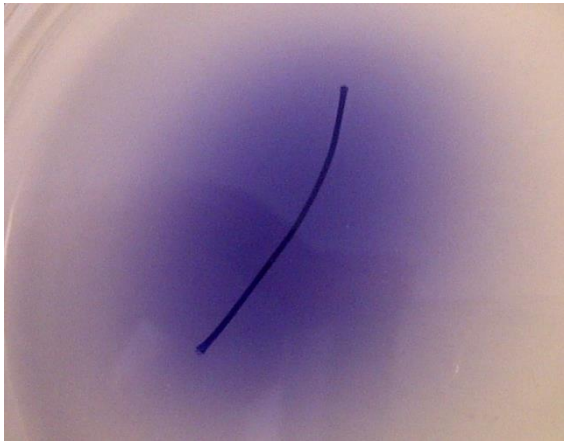
What's On the Horizon?

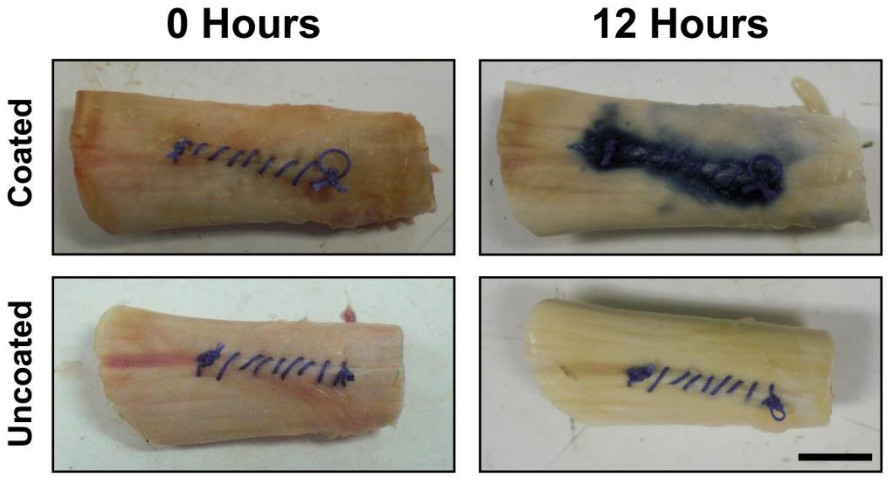
Annulus Repair

- Agent is rapidly released from suture/device coating
- Repair strength **doubled**



Release of agent from suture coating





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Acknowledgements

Researchers/Collaborators:

Matt Brown, Ph.D.
John Racadio, MD
Sharath Sundararaj, Ph.D.
Stephanie Hunt, MS
Todd Abruzzo, MD
Paul Slusarewicz, Ph.D.
Joe Bader, Ph.D.
Richard Smith, BS, DO
Bryan Kirking, Ph.D.
John Criscione, Ph.D.
Karin Swartz, M.D.
Christopher Chaput, MD.
Gerhardt Friehs, MD
Brendan Chuang, MD, Ph.D.
John Popovich, DPT, Ph.D.
Justin Toungate, BS
Keng Zhu, Ph.D.
Jonathan Golightly, MS
David Yau, M.D.
Bo Han, Ph.D.
Dean Gray, MS
Howard Loree, Ph.D.
Russell Odono, MD
Varun Bharwaj, MS, J.D.
Baber Syed, MS

Grants/Institutional:

NIH-NIAMS, SBIR/STTR Grants (4)
Kentucky SBIR Matching Grants (2)
University of Southern California
University of Kentucky

Private:

Orthopeutics, LP
Intralink-Spine, Inc.

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