A2M: The End of Steroid Injections!

Gaetano J Scuderi, MD
Disclosure
Key Points

• EPIDURAL STEROID INJECTION (ESI)
• MOST COMMON TX FOR LBP
• Never FDA APPROVED!
• SIDE EFFECTS/COMPLICATIONS (why?)
• ARCHAIC

A SIMPLE TEST CAN PREDICT WHO GETS BETTER

ALPHA-2-MACROGLOBULIN (A2M) IS THE FUTURE
ESI

- Most utilized pain management procedure in world
- Considerable controversy surrounding safety/efficacy
- Modest effect size <3 months in well-selected Patients
- Serious complications are rare

- Guidelines suggest that the # of injections should be tailored to individual response, rather than a set series.

Complications may be serious

- Spine J. 2016. Preoperative epidural injections are associated with increased risk of infection after single-level lumbar decompression.

- Pain Physician. 2015. Immediate and acute adverse effects following transforaminal epidural steroid injections with dexamethasone.


The List is Long

- Localized increase in pain
- Dural punctures
- Extremity weakness
- Nausea
- Pruritus
- Non-positional headaches
- Facial flushing
- Anxiety
- Sleeplessness
- High blood sugar

- Fever the night of injection
- Transient decrease in immunity
- Stomach ulcers
- Severe arthritis of the hips (avascular necrosis)
- Surgical infection risk
- Ophthalmologic issues
- Cataracts
- Skin depigmentation
- Osteoporosis
Who can forget this?
70 Deaths, hundreds of cases

Fungal Meningitis and Steroid Injections: a Health-Care Disease...
www.medicinenet.com › ... › infectious disease az list ▼ MedicineNet ▼
A new health-care-related disease has been identified by the U.S. Centers for Disease Control and Prevention (CDC). ... While it is not new per se, it was newly found to be health-care-related because the disease is linked to a treatment known as epidural steroid injections, a ...

Fungal Meningitis Outbreak 2012 - New England Journal of M...
www.nejm.org/.../fungal-meningit... ▼ The New England Journal of Medicine ▼
In September, a patient in Tennessee died unexpectedly from fungal meningitis. An epidural glucocorticoid injection was identified as a potential source of this ...

Unraveling the largest outbreak of fungal infections ... - Scienc...
www.sciencedaily.com/releases/2013/.../130626113519.ht... ▼ Science Daily ▼
Jun 26, 2013 - ... and Prevention describe pathologic findings from 40 case reports of fungal infection in patients who had been given contaminated epidural, ...

Unraveling the Largest Outbreak of Fungal Infections ... - Else...
https://www.elsevier.com/.../unraveling-the-largest-outbreak-of-f ▼ Elsevier ▼
FDA Status

Not FDA-Approved

- The steroids used in epidural steroid injections are FDA-approved for your muscles and joints, but the FDA has never approved the injections for spinal use.

Doctors are allowed to use drugs for other purposes than those they were originally approved for -- this is called “off-label use” – but that means that use never underwent an official study to make sure it’s safe and effective. Even so, Medicare covers ESIs and insurance companies also pay for many of them.
Uses for Steroids

• systemic vasculitis (inflammation of blood vessels) myositis (inflammation of muscle), rheumatoid arthritis, lupus, Sjögren's syndrome, gout, osteoarthritis, temporal arteritis, dermatitis, allergic reactions, blood disorders, asthma, hepatitis, inflammatory bowel disease (ulcerative colitis and Crohn's disease), sarcoidosis, traumatic brain injury, conjunctivitis, tendonitis, fasciitis, pruritus, eczema, psoriasis, immune disorders, COPD, bronchitis, shock, spinal injury, cancers.
Let's face the facts, steroids are archaic. We have needed a physiologic approach to treatment for decades.
The MRI Enigma

• MRI identifies many age related “abnormalities”
• Challenging for Physician to interpret MRI as the source of a patient’s pain
Causes of Sciatica

- **Mechanical root compression by Herniated Nuclues Pulposis (HNP)**
  - Carragee & Kim (Spine 1996): *Size of HNP* and *acuity of symptoms* correlates with outcome
- **Chemical/inflammatory**
  - Kang, and et al. (Spine 1996):
    - Herniated discs have increase
    - MMPs, NO, PGE, IL-6
- **Primary nerve injury**
  - Chronic radiculitis
  - rhBMP-2 injury
- **Non-spinal etiologies**
  - Hip/pelvic pathology
Brief Review of Discovery

1) We discovered a cartilage based protein complex that is only present in the synovial fluid, disc and epidural space in patients with pain.

2) This complex was shown to be associated with neurological irritation and joint pain and recently, early OA.

3) We have developed a specific ELISA assay to measure the presence of the protein complex.

4) It is a target for development of therapeutics for cartilage injuries causing pain.
Identification of a complex between fibronectin and aggrecan G3 domain in synovial fluid of patients with painful meniscal pathology

Gaetano J. Scuderi, Naruewan Woolf, Kaitlyn Dent, S. Raymond Golish, Jason Cuellar, Vanessa Cuellar, David Yeomans, Eugene J. Carragee, Martin Angst, Robert Bowser, Lewis S. Hanna
FA ELISA

- **C** = Healthy control
- **P** = Patient with pain

Graph showing O.D. (450nm) for subjects C1 to C12 and P1 to P12.
Identification of a Novel Fibronectin-Aggreican Complex in the Synovial Fluid of Knees with Painful Meniscal Injury

By Gaetano J. Scuderi, MD, S. Raymond Golish, MD, PhD, Frank F. Cook, MD, Jason M. Cuellar, MD, PhD, Robert P. Bowser, PhD, and Lewis S. Hanna, PhD

Investigation performed at Jupiter Outpatient Medical Center, Jupiter, Florida
Results

Fig. 1
Bar graph depicting the level of the fibronectin-aggre can complex in the study and control groups. The values on the y axis indicate the mean optical density at a 450-nm optical wavelength for the heterogeneous ELISA on a logarithm base 10 scale. The error bars represent the standard error of the mean.
ROC for diagnostic
Lumbar ESI
Fibronectin and Aggrecan G3

• Prospective, consecutive
• Radiculopathic pain and MRI + for HNP
• Symptoms consistent with radiculopathy
• Lavage with NS was performed immediately prior to ESI
• Fluid was assayed for the FAC complex
• SF-36 p injection compared with baseline
Identifying “Responders”

**Mean SF-36 Improvement 20.4 (95% CI)**
Functional Outcomes after Lumbar Epidural Steroid Injection Is Predicted By A Complex of Fibronectin and Aggrecan

S. Raymond Golish MD PhD†, Lewis S. Hanna PhD‡, Robert P. Bowser PhD ◦, Pasquale X. Montesano MD ‡, Eugene J. Carragee MD†, Gaetano J. Scuderi MD†

SPINE 2011
Fibronectin-Aggregan Complex as a Marker for Cartilage Degradation in Non-Arthritic Hips?


KSSTA 2014
HIP pain ROC Curve w/o Radiographic OA
Functional Outcome after Lumbar Discectomy is Predicted by a Complex of Fibronectin and Aggrecan

Micah Smith MD†, Agnes Ith MD†, Eugene J. Carragee MD†, Ivan Cheng MD†, Todd F. Alamin MD†, Lewis S. Hanna PhD‡, S. Raymond Golish MD PhD†, Gaetano J. Scuderi MD†
Study Design

- Single center, prospective, consecutive study
- 4 spine surgeons
- Cytokine sampling techniques:
  - Excised disc fragment underwent lavage
  - Assayed for the fibronectin-aggrecean complex (FAC)
- Outcome metrics:
  - Oswestry Disability Index (ODI) baseline/3 month follow-up.
  - Visual Analog Scores (VAS) baseline/3 month follow-up
- Primary Outcome: “Better” defined as BOTH VAS decrease >=3 and ODI of > 20 points.
ODI

Pre-op: 52.9
Post-op: 13.3
Average Change: 39.6

p<0.000001

VAS

Pre-op: 6.8
Post-op: 2.1
Average Change: 4.7

p<0.000001
Results: FAC as Prognostic Test

- Clinical Improvement Composite
  - ODI decrease >=20 AND
  - VAS decrease >=3
- AUC = 0.66 ± 0.077
- p = 0.037
- N = 75
Conclusions

• We found a high PPV for the presence of FAC at surgical discectomy and substantial clinical improvement (85%)
• The presence of FAC during open discectomy is associated with improvement (p=0.02)
• Presence of FAC as well as weakness associated with improved outcomes
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fibronectin-Aggregan Complex as a Marker for Cartilage Degradation in Non-Arthritic Hips</td>
<td>Abrams, Safran, Shapiro, Maloney, Goodman, Huddleston, Bellino, Scuderi</td>
<td>Knee Surgery, Sports Traumatology, Arthroscopy Journal</td>
<td>January-14</td>
</tr>
<tr>
<td>2</td>
<td>Does the Presence of the Fibronectin-Aggregan Complex Predict Outcomes from Lumber Discectomy for Disc Herniation?</td>
<td>Scuderi, Cheng, Amin, Carragee, Smuck, Martinez, Mitsuhashi, Mitsuhashi, Smith</td>
<td>The Spine Journal</td>
<td>November-13</td>
</tr>
<tr>
<td>3</td>
<td>Does a Fibronectin and Aggregan Complex Play a Role in Painful Vertebral Disks?</td>
<td>Cuelar, Golish, Leroux, Reuter, Carragee, Hanna, Scuderi</td>
<td>PM&amp;R Journal</td>
<td>April-13</td>
</tr>
<tr>
<td>4</td>
<td>Cytokine Expression in the Epidural Space: A Model of Non-Compressive Disc Herniation Induced Inflammation</td>
<td>Cuelar, Borges, Cuelar, Yoo, Scuderi, Yeomans</td>
<td>SPINE</td>
<td>September-12</td>
</tr>
<tr>
<td>5</td>
<td>Ankle Intraarticular Pathology Correlation With Cytokine Inflammatory Biomarkers And Degradation Products</td>
<td>San Giovanni, Golish, Hanna, Scuderi</td>
<td>Foot &amp; Ankle International</td>
<td>June-12</td>
</tr>
<tr>
<td>6</td>
<td>The Fibronectin-Aggregan Complex: Is It Present in Cervical Disc Disease?</td>
<td>Gajendra, Reuter, Golish, Hanna, Scuderi</td>
<td>PM&amp;R Journal</td>
<td>November-11</td>
</tr>
<tr>
<td>7</td>
<td>Clinically Significant Improvement in Functional Outcome after Lumbar Epidural Steroid Injection for Radiculopathy Is Predicted By Assay for Novel Fibronectin-Aggregan Complex</td>
<td>Golish, Hanna, Bowser, Montesano, Carragee, Scuderi</td>
<td>SPINE</td>
<td>August-11</td>
</tr>
<tr>
<td>8</td>
<td>Identification of a Novel Fibronectin-Aggregan Complex in the Synovial Fluid of Knees with Painful Meniscal Injury</td>
<td>Scuderi, Golish, Bowser, Cook, Cuelar, Hanna</td>
<td>Journal of Bone &amp; Joint Surgery</td>
<td>February-11</td>
</tr>
<tr>
<td>9</td>
<td>Cytokine Profiling in Acute Anterior Cruciate Ligament Injury</td>
<td>Cuelar, Cuelar, Golish, Yeomans, Scuderi</td>
<td>ARTHROSCOPY</td>
<td>October-10</td>
</tr>
<tr>
<td>10</td>
<td>Identification of a Complex of Structural Proteins in Synovial Fluid of Patients with Painful Meniscal Pathology</td>
<td>Scuderi, Woof, Dent, Golish, Cuelar, Cuelar, Yeomans, Carragee, Angst, Bowser, Hanna</td>
<td>Clinical Biochemistry</td>
<td>July-10</td>
</tr>
<tr>
<td>11</td>
<td>Cytokine Evaluation in Individuals with Low Back Pain Utilizing Discographic Lavage</td>
<td>Cuelar, Golish, Reuter, Cuelar, Angst, Carragee, Yeomans, Scuderi</td>
<td>The Spine Journal</td>
<td>March-10</td>
</tr>
<tr>
<td>12</td>
<td>Diagnostic Utility of Cytokine Biomarkers in the Evaluation of Acute Knee Pain</td>
<td>Cuelar, Scuderi, Gabrovsky-Cuellar, Golish, Yeomans, Angst</td>
<td>Journal of Bone &amp; Joint Surgery</td>
<td>October-09</td>
</tr>
<tr>
<td>13</td>
<td>Epidural Interferon Gamma-Immunoreactivity: a Biomarker for Lumbar Nerve Root Irritation</td>
<td>Scuderi, Cuelar, Cuelar, Yeomans, Carragee, Angst</td>
<td>SPINE</td>
<td>October-09</td>
</tr>
<tr>
<td>14</td>
<td>A Critical Evaluation of Discography in Patients with Lumbar Intervertebral Disk Disease</td>
<td>Scuderi, Brusovanik, Golish, DeMec, Hyde, Hallab, Vaccaro</td>
<td>The Spine Journal</td>
<td>October-08</td>
</tr>
<tr>
<td>15</td>
<td>Cytokine Assay of Epidural Space Lavage in Patients with Lumbar Intervertebral Disk Herniation and Radiculopathy</td>
<td>Scuderi, Brusovanik, Anderson, DeMec, Vaccaro</td>
<td>Journal of Spinal Disorders &amp; Techniques</td>
<td>April-06</td>
</tr>
</tbody>
</table>
FACT™

A marker for painful Cartilage Lesions
FAC assembly exposes the G3 CRP domain, a potential DAMP

1) Resident leukocytes are activated by DAMPs or PAMPs, caused by tissue damage or pathogens.
FAC assembly exposes the G3 CRP domain, a potential DAMP

1) Resident leukocytes are activated by DAMPs or PAMPs, caused by tissue damage or pathogens

2) Activated leukocytes secrete pro-inflammatory cytokines, MMPs and ADAMTSs

3) MMPs and ADAMTS proteases cleave Aggrecan, leading to G3 fragments

1) Resident leukocytes

2) Activated leukocytes

3) MMP/ADAMTS

Confidential, Property of Cytonics Corp
FAC assembly exposes the G3 CRP domain, a potential DAMP

4) Fibronectin binds to the Aggrecan G3 Lectin binding domain, causing a conformational shift that exposes the CRP domain

5) CRP domain of Aggrecan acts as a DAMP, recognized by leukocytes
FAC assembly exposes the G3 CRP domain, a potential DAMP
Normal Cartilage Metabolism

- Highly regulated balance: synthesis vs degradation
Pathophysiology of DJD

Biomechanical Mediators

Biochemical Mediators

Fibroblasts

Endothelial cells

Macrophages

Other cells

Osteoclasts

Osteoblasts

Chondrocytes

Pro-Inflammatory Cytokines (TNFα, IL-1β)

MMP

ADAMTS

ECM fragments

Osteophyte
Overlapping Pathophysiologic Theories of OA:

• 1) Biomechanical (overweight, injury, etc)
  • Biomechanical insults activate the biochemical pathway (chondrocyte activation, protease release)

• 2) Biochemical (cartilage degradation, lesions, chondrocyte activation and protease release, inflammation)
  • Biochemical insults reinforce the biomechanical pathway (instability, degradation, pain)
Overlapping Pathophysiologic Theories of OA:

• 1) Biomechanical (overweight, injury, etc)
  • Biomechanical insults activate the biochemical pathway (chondrocyte activation, protease release)
  • Treated with surgery, physical therapy

• 2) Biochemical (cartilage degradation, lesions, chondrocyte activation and protease release, inflammation)
  • Biochemical insults reinforce the biomechanical pathway (instability, degradation, pain)
  • Treatment: Current drugs treat pain and/or inflammation indirectly. Attempts at biologic treatment with mixed results (e.g. anti-TNF-alpha approach).
OA is a complex web

IL-1

MMP-3

ADAMTS-5
OA has *Lots* of Crosstalk
OA known to involve inflammatory mediators and proteases

- Pro-Inflammatory Cytokines Degrade Cartilage (i.e. IL-1, IL-6, TNFα, INFγ, MIP, MCP, etc...)

- Metalloprotease Enzymes Breakdown Cartilage (i.e. MMP’s 1,3,9,13, etc...)

- Disintegrin Proteins Cleave Cartilage (i.e. ADAMTS 4,5 etc...)
α-2-Macroglobulin

1. A-2-Macroglobulin (A2M) is a tetramer (720KDa) with monomers connected by disulfide bonds and dimers connected by hydrophobic interactions

2. A2M has a bait region, that upon cleavage, induces a conformation change trapping the protease

3. The bait region has a random coil structure

4. It is well known that wild-type A2M has different affinities for multiple substrates but could be optimized for a specific pathophysiologic cascade
\(\alpha-2\)-Macroglobulin Inhibition of Proteases

Proteases

Active
A2M

A2M + Proteases

A2M-Protease Complex
Pathophysiology of DJD

Biomechanical Mediators

Fibroblasts

Biochemical Mediators

Endothelial cells

Pro-Inflammatory Cytokines (TNFα, IL-1β)

Macrophages

Chondrocytes

Other cells

MMP ADAMTS

A2M

ECM fragments

Osteoclasts

Osteophyte

Osteoblasts
A Model for Cartilage Degradation

- Laboratory model for testing molecules that stop cartilage loss.
Preclinical Data: Cartilage Explants

- Bovine Cartilage Explant (BCE) ex vivo model
  - Cartilage pieces with live chondrocytes are cultured
  - Addition of TNF\(\alpha\) and IL-1\(\beta\) induce activation of chondrocytes and production of MMPs and ADAMTSs.
  - Cartilage catabolism is followed in the culture media with a dye that binds sulfated glycosaminoglycans (sGAG).
A2M Inhibition of Protease and Cytokine Induced Cartilage Catabolism

BCE
Cytokines
Purified A2M
A2M Inhibition of MMP-7 and MMP-12-digestion of Cartilage

- BCE were treated with 5ug/ml MMP-7 or MMP-12, with or without 100ug/ml Purified A2M

Results: BCE digestion was blocked by purified A2M.
A2M Inhibition of ADAMTS-5-digestion of Cartilage

- SDS-PAGE fractionation of proteins, visualized using Bio-Rad “stain free” system
- Several proteins were observed in ADAMTS-5-digested BCE
- BCE treated with ADAMTS-5 produces an Aggrecan G3 fragment
- The G3 fragment is known to form a complex with Fibronectin, detectable by ELISA
- Since A2M treatment reduces the G3 fragment, treatment with APIC may lower FAC formation
Autologous Protease Inhibitor Technology

- Tangential Flow Filter technology allows selective filtration without clogging pores
• Addition of APIC inhibited TNFα/IL-1β-induced cartilage catabolism in a dose-dependent manner
Post Traumatic OA Model: ACL-T *In vivo*

- Treatment and Control Groups
- Injections at 1, 4, and 14 days

**Strong Evidence APIC Reduces PTOA**
Autologous Therapeutic
Novel tangential flow technology
Concentrates A2M
510k Device
Increasing Awareness

Identification of $\alpha_2$-Macroglobulin as a Master Inhibitor of Cartilage-Degrading Factors That Attenuates the Progression of Posttraumatic Osteoarthritis

Shaowei Wang,1 Xiaoqun Wei,2 Jingming Zhou,3 Jing Zhang,4 Kai Li,5 Qian Chen,3 Richard Terek,3 Braden C. Fleming,3 Mary B. Goldring,6 Michael G. Ehrlich,3 Ge Zhang,7 and Lei Wei5
Conclusion

In summary, up-regulation of cartilage catabolic cytokines and enzymes is thought to be a key mechanism of cartilage damage. Thus, inhibition of these molecules will likely slow or prevent the progression of disease. Our novel data indicate that $\alpha_2$M is a master inhibitor of many types of cartilage-degrading enzymes and that it acts not only by blocking activity, but also by decreasing gene expression and protein levels in the joint. The innate levels of $\alpha_2$M in SF may not be sufficient to reduce the activities of catabolic enzymes that are present after joint injury. In this study, supplemental intraarticular injection of $\alpha_2$M attenuated cartilage degeneration in a rat model of ACLT, suggesting that it may be a potential novel therapy for posttraumatic OA.
APIC CF Phase I/II Clinical Study

- Treatment of Mild to Moderate OA
- Currently:
  - 126 Patients enrolled
  - 11 Trial Sites
- Interim Analysis in June 2016
- No Adverse events to date.

*On Label Indication for Tx of OA
Surrogate Human Safety and Efficacy Data for Recombinant A2M Product*
The Real Goal

• Off the shelf product
• Recombinant based
• No need for Blood draws
• Easy Access
• Easy Dosing for different joints
• Able to Dose Multiple Sites
Small Animal Model — Summary

Rat ACL Transection Model (n=77)
- 7-arms, parallel group
- 11 animals per arm
- OARSI cartilage degeneration score
- Score 0–15 (0–5 x 3 zones)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage degeneration</td>
<td>0</td>
<td>No degeneration</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minimal degeneration; 5–10% of the total projected cartilage area affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by matrix or chondrocyte loss</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Mild degeneration; 11–25% affected</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate degeneration; 26–50% affected</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Marked degeneration; 51–75% affected</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Severe degeneration; greater than 75% affected</td>
</tr>
</tbody>
</table>

Mean ±/1 SD

- Positive control
- Negative control
- Wild-type
- Variant 1 low dose
- Variant 1 high dose
- Variant 2 low dose
- Variant 2 high dose
Positive control  Negative control  Wild-type  Variant 1 low dose  Variant 1 high dose  Variant 2 low dose  Variant 2 high dose

Optimized Variant
• Clearly superior to wild-type
• Very large effect size (Cohen’s $d = 1.87$)
• Highly statistically significant ($p < 0.001$)

• Causes cartilage degeneration to go from moderate in untreated animals to minimal in treated animals!
Cartilage Regrowth?

# Compared with ACLT + saline, P≤0.05
* Compared with sham, P≤0.05
& Compared with ACLT+A2M, P≤0.05
€ Compared with ACLT+98-2-L, P≤0.05
β Compared with ACLT+98-2-H, P≤0.05
α Compared with ACLT+108-2-L, P≤0.05

# Compared with ACLT + saline, P≤0.05
* Compared with sham, P≤0.05
& Compared with ACLT+A2M, P≤0.05
€ Compared with ACLT+98-2-L, P≤0.05
β Compared with ACLT+98-2-H, P≤0.05
α Compared with ACLT+108-2-L, P≤0.05

Fig. 6E and F. RT-PCR
Fibronectin-Aggreccan Complex (FAC) As a Predictor of Back Pain Relief After Intradiscal Injection of Autologous Alpha-2-Macroglobulin (A2M)
Purpose:

• Determine the ability of FAC to predict response to biologic therapy with concentrated autologous A2M for patients with LBP from DDD
• Study Design/Setting: Prospective cohort
• Patient Sample: 24 patients with LBP pain and MRI positive for DDD
Results:

• 24 Patients with LBP
• 13 males and 11 females.
• Age range 24-62 (ave 44.3)
• 13 pts had 1 level, 6 pts 2 level, and 5, 3 level procedures.
Results:

• 12 discs FAC + out of 40 discs tested

• 10 patients out of 24 had “Discogenic” source of pain by FAC
Clinical follow-up time point
**Oswestry Disability Index**

![Graph showing Oswestry Disability Index over time with Pre-op ODI, 12 wk ODI, and 24 wk ODI for FACT-Negative and FACT-Positive categories. The graph indicates a decrease in ODI from Pre-op to 24 wk ODI for both categories, with a notable increase in FACT-Positive from 12 wk to 24 wk ODI.](image-url)
Discussion:

- Patients who are “FACT+” are more likely to demonstrate clinical improvement following autologous A2M injection.
- The results of this investigation suggest that not only is FAC an important biomarker in identifying who will improve, but also that autologous A2M is an important biologic treatment in discogenic diseases, a true theranostic.
Conclusions

• Currently, there are few efficacious treatments that address the biochemical mediators in mild to moderate OA, DDD, HNP

• Injecting autologous wild-type A2M represents a novel therapeutic approach to treating cartilage based disease

• Autologous Protease Inhibitor Concentrate (APIC) blocks cartilage catabolism in vitro and in vivo

• Recombinant A2M is efficacious for OA/DJD with evidence of cartilage growth in synovial joints
Points to Remember

• ESI MOST COMMON TX FOR Lumbar syndromes
• Steroids are ARCHAIC, with systemic effects in all tissues.
• It’s time for a physiologic treatment

FACT improves efficacy of treatment

ALPHA-2-MACROGLOBULIN (A2M) IS HERE!