

Poly-gamma-glutamic acid as a novel material for viscosupplementation and treating OA of the knee – A pilot study

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Disclosure:

Study funded by Crescent Innovations Inc.

Presented by Al Prescott, President and
Founder





Helping Manage Pain

Osteoarthritis

- ***Incurable and chronic form of arthritis.***
- ***Characterized by a breakdown of cartilage and synovial fluid in the joints.***
- ***Resulting in (or caused by) inflammation.***
- ***In U.S., 12% of US adults between the ages of 25 and 74 years.***
- ***Globally, prevalence estimates were 1-80%, although most were 5-25%.***

J Am Osteopath Assoc. 2001 Apr;101(4 Suppl Pt 2):S2-5.

Semin Arthritis Rheum. 2014 Jun;43(6):713-20. doi: 10.1016/j.semarthrit.2013.12.007. Epub 2013 Dec 31.

Osteoarthritis – Risk Factors

- **Age - 80% of persons older than 75 years**
- **Obesity - women who lost average of 11 pounds decreased their risk up to 50%**
- **Joint Injury - Jobs requiring simultaneous squatting and turning may cause up to 30% of knee OA in men.**
- **Muscle weakness**
- **Ethnic characteristics**
- **Nutritional factors**
- **Genetics**

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Weight loss reduces the risk for symptomatic knee osteoarthritis in women. Ann Intern Med 1992;166:535-539



Osteoarthritis – Nonpharmacologic Treatments

- ***Weight loss***
- ***Physical therapy***
- ***Occupational therapy***
- ***Patient education***
- ***Aerobic conditioning exercises***
- ***Assistive devices/footwear***

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Osteoarthritis – Pharmacological Treatments

Systemic treatment modalities

- **Nonopioid analgesics**
- **Nonsteroidal anti-inflammatory drugs**
- **Opioid analgesics**
- **Glucosamine and chondroitin sulfate**
- ***7 Intra-articular therapy***
 - **Corticosteroids**
 - **Viscosupplementation**
- ***Topical analgesics***
- ***Joint Replacement***

Viscosupplementation



All have 1 key ingredient – Hyaluronic Acid / Sodium Hyaluronate

Adverse Reactions – Joint Pain/swelling

Product/Study	Hyaluronic Acid	Placebo
Hyalgan	23% (1.8x)	13%
Synvisc One	4.9% (3.3x)	1.5%
Orthovisc	2.5% (1.3x)	2.0%

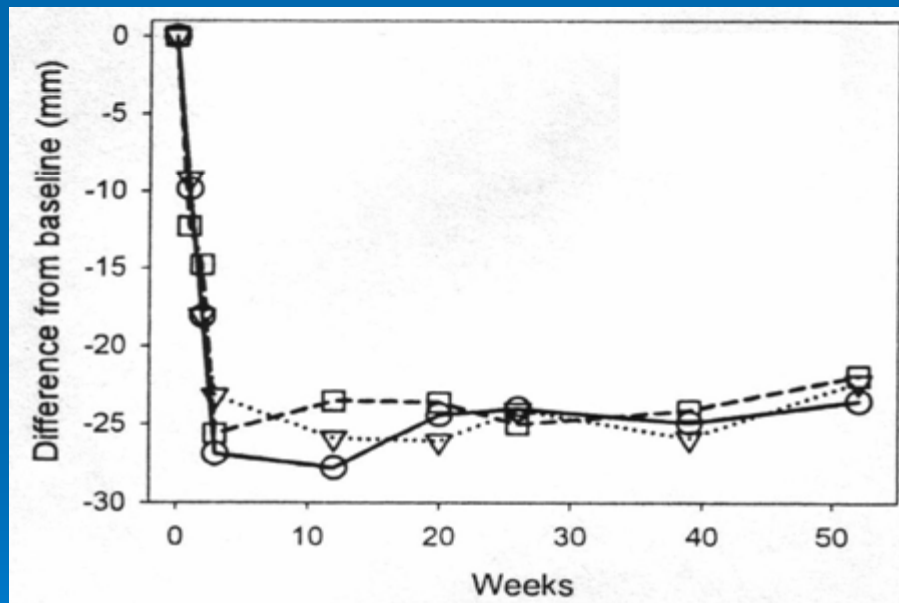
Why?

All hyaluronic acids are either:

Avian tissue extracted, or
Fermented via bacterial pathogen.

Viscosupplementation - Performance

All Made with Hyaluronic Acid, and all perform...



...the same.

Rheumatology 2002;41:1240-1248

Viscosupplementation

In the event that an alternate material could be shown to be:

- *Non-inflammatory,*
- *Non-immunogenic,*
- *Non-cytotoxic, AND*
- *Able to reduce inflammation*

Chronic Osteoarthritis

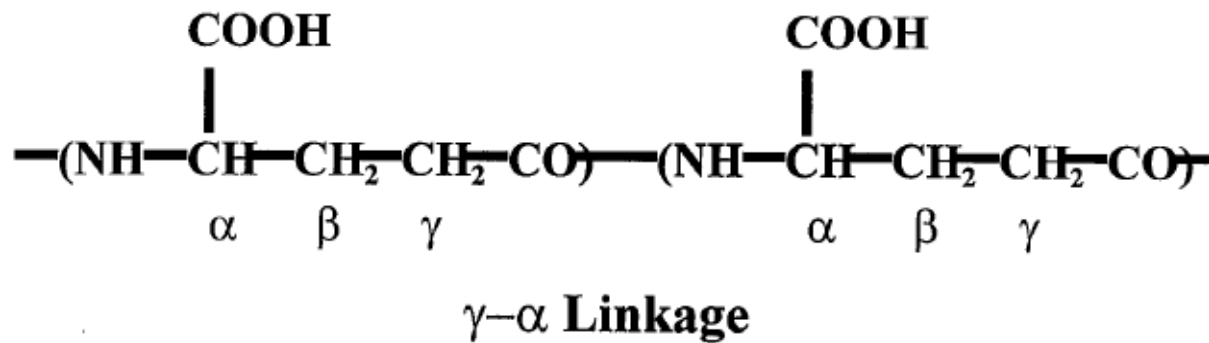
➤ *Inflammation*



Inflammation can be
measured by collagenase
MMPs (1,8, 13*)

New Material

- *How do we propose to reduce inflammation?*



gPGA – poly-gamma-glutamic acid

gPGA

- *gPGA was produced by fermenting a non-pathogenic Bacillus.*
- *gPGA was purified via filtration and buffer exchange and formulated using sterile saline for injection at a concentration of 30 mg/ml.*
- *The molecular weight was determined to be 1.22 million Daltons with a polydispersity of 1.1 using HPLC and MALLS.*
- *gPGA viscosity was measured at 4,900 cps on a Brookfield viscometer using a CP-52 spindle at an rpm of 0.5*

Pre-Clinical Safety Data

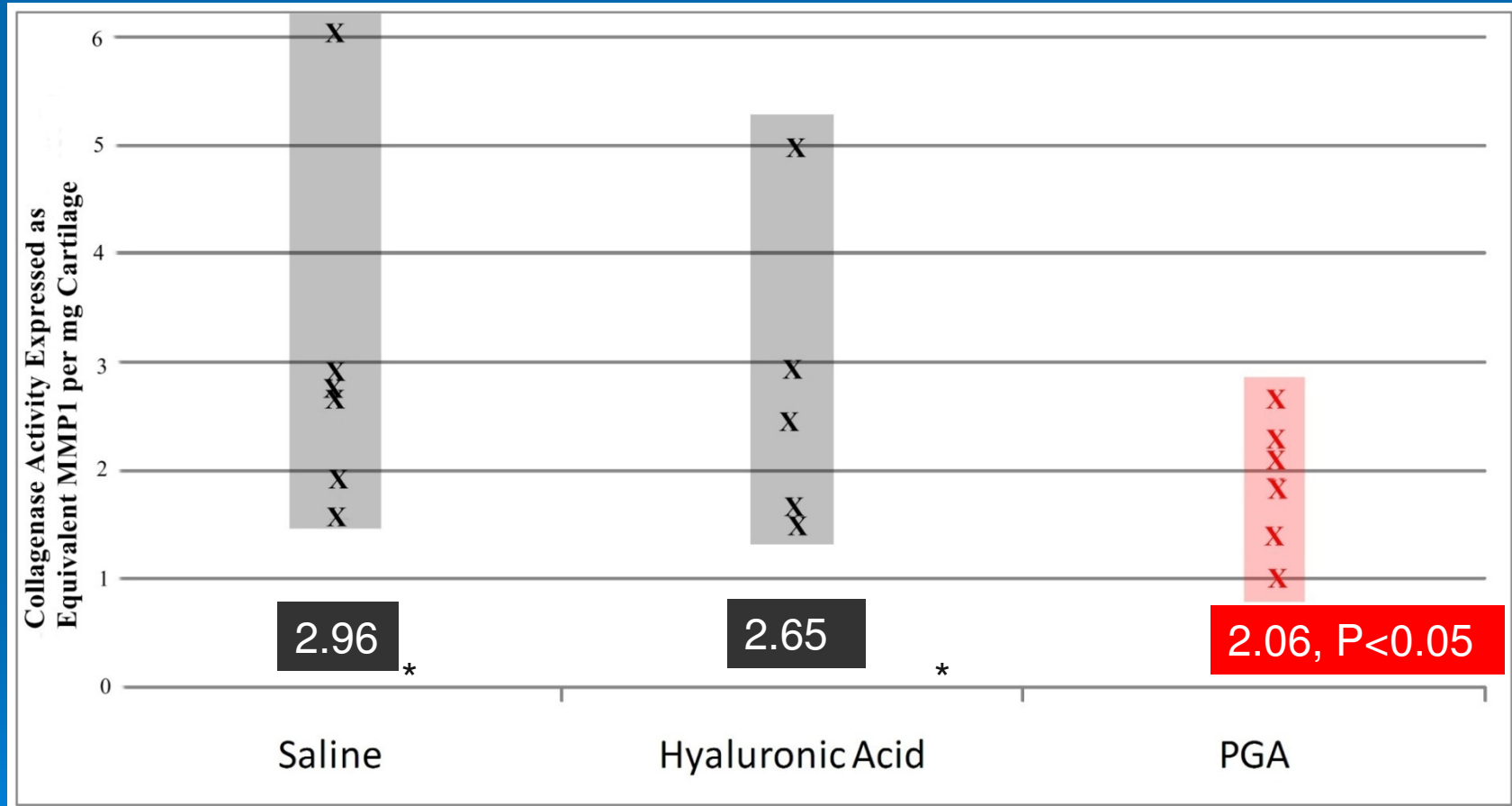
Have Passed ISO Standards for:

- *Cytotoxicity*
- *Sensitization / Irritation*
- *Intracutaneous – Direct*
- *Systemic Toxicity*
- *Rabbit Pyrogen*
- *Genotoxicity*
- *Hemocompatibility*
- *Hemolysis*
- *Implantation*
- *Generally Regarded as Safe - GRAS*

MMP Study Design

- *18 rats were divided into 3 groups of six.*
- *All rats had their left knee injected with monoiodoacetate (MIA)[Kim 2012].*
- *7 days later the rats were treated with a single 50 uL injection, in that knee, of either saline, Hyalgan®(a commercially approved HA), or gPGA.*
- *At Day 9, all animals were sacrificed, the hind limbs disarticulated, and the cartilage removed.*
- *Collagenase MMPs were extracted using a two step procedure described in Janusz.*
- *Results were reported as equivalent MMP-1 activity per mg cartilage.*

Results

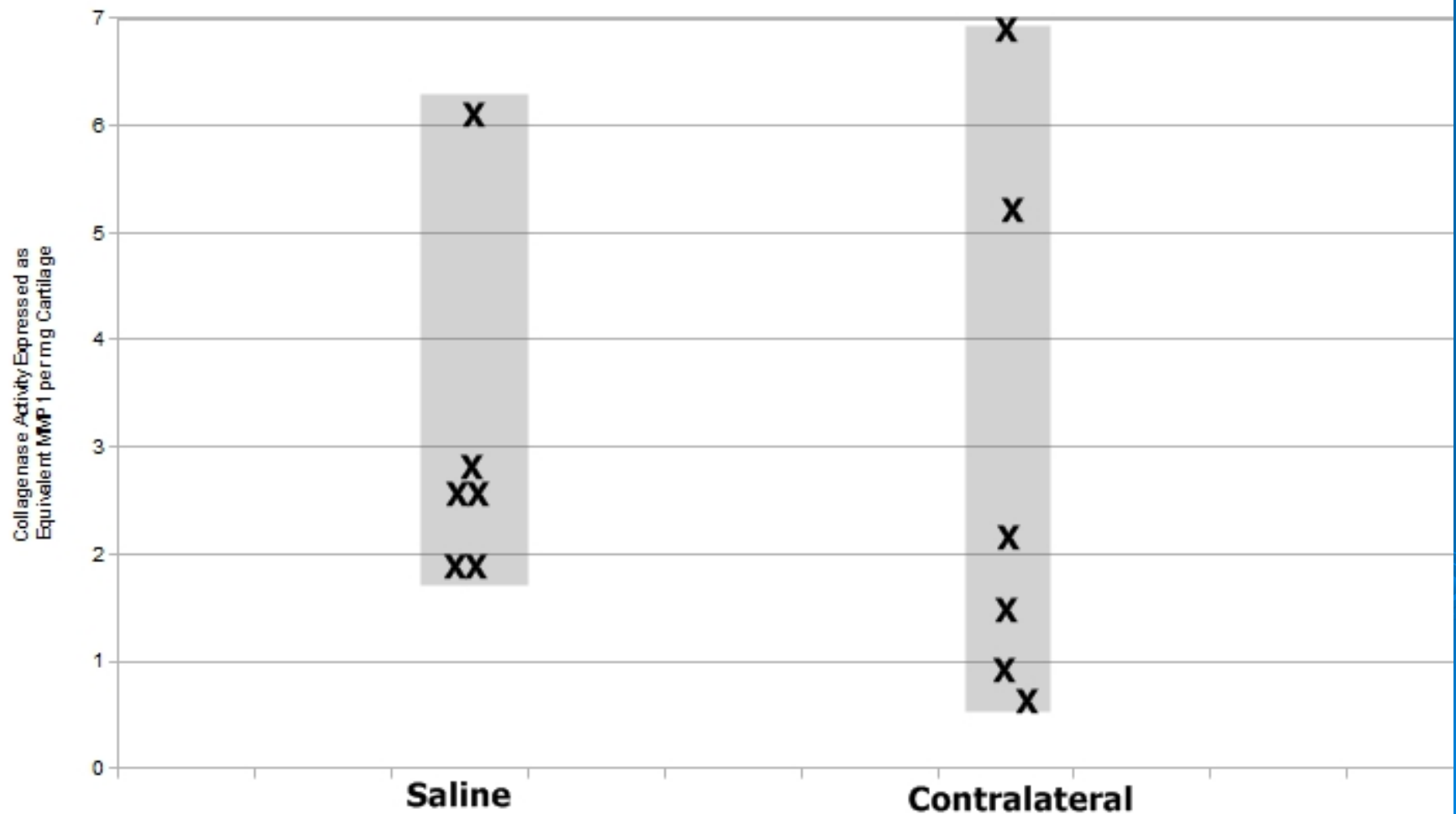


Note: Hyaluronic Acid group contained a single animal that tested at 17.8 MMP1/mg cartilage

Additional Thoughts - Outlier

- ***It is possible that the single large MMP value in the Hyalgan group is evidence of an adverse reaction to Hyalgan.***
- ***It is known that HA is associated with elevated adverse reaction rates in the human population compared to saline treatments.***
 - Hyalgan had 23% of the patients (38 out of 164) reported pain at the injection site, as compared to 13% (22 out of 168) in the saline placebo treated group.
 - 23% out of 6 animals is 1.38, so on the surface, having 1 animal with elevated levels of an OA related MMP might not be out of the question.
 - Remains speculation since there is no corroborating evidence of adverse reactions of HA in rats.
 - If, however, we accept that elevated MMPs are a marker of inflammation, and the single value that is almost 10x the average of the group constitutes an adverse reaction, then it is worth noting that the PGA group does NOT contain a similar point. This may suggest that PGA has a better safety profile than HA for treating OA of the knee.

Additional Thoughts – Contralateral Data



Additional Thoughts – Chicken or Egg?

- ***Why does viscosupplementation work?***
 - Mechanical?
 - Biological?
 - Other?

Efficacy – Traditional Thoughts

Justification for Viscosupplementation (mechanical)

- *Cushioning*
- *Lubrication*
- *Replacement of degraded hyaluronic acid*
- *“The results indicate that proteoglycan subunit has a clearance half life of around 12 hours in normal joints and that this rate is not significantly altered in the presence of an active synovitis.” Page-Thomas.*
- *“Pulse chase experiments of intracellular hyaluronan suggest the half-life of internalized HA is 2-3 hours.”
Tammi*

Efficacy – Crescent Innovations' Thoughts

Degenerative Joint Disease

➤ *Injury*

➤ *Inflammation*

➤ *Joint Degradation*

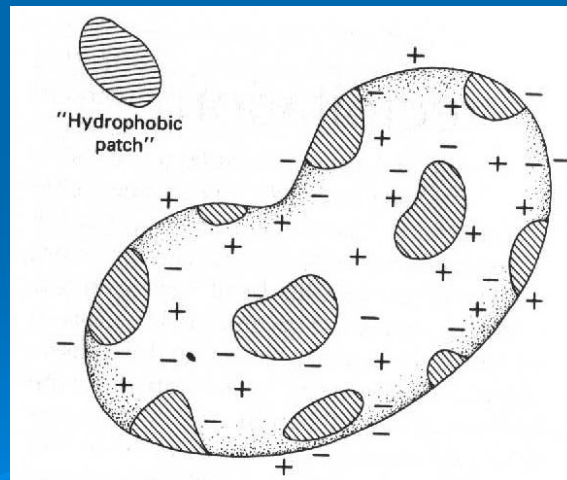


Efficacy – Crescent Innovations' Thoughts

➤ *Inflammatory Markers*

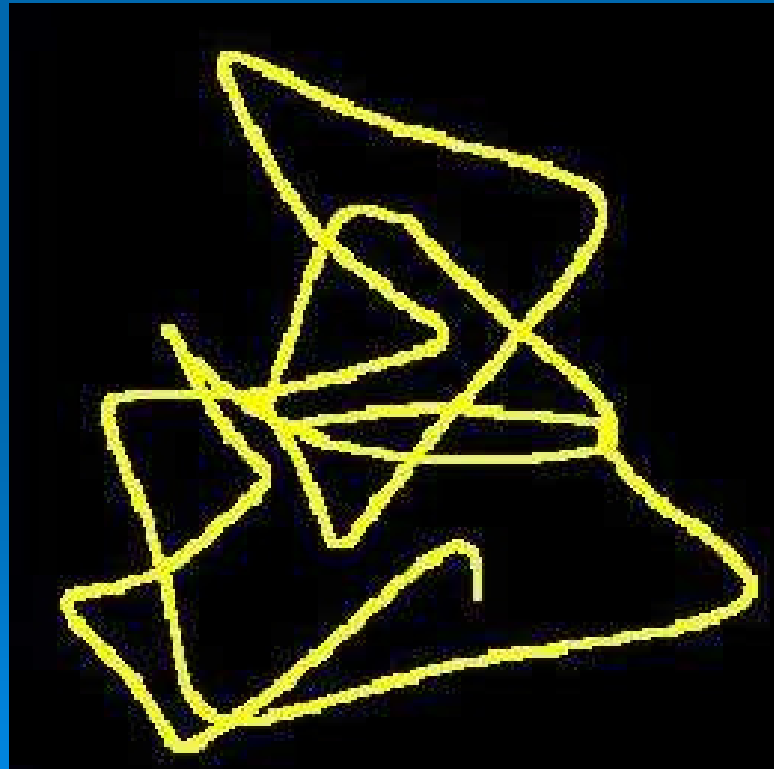
- Cytokines
- Matrix-metallo-proteinases

➤ *All Proteins*

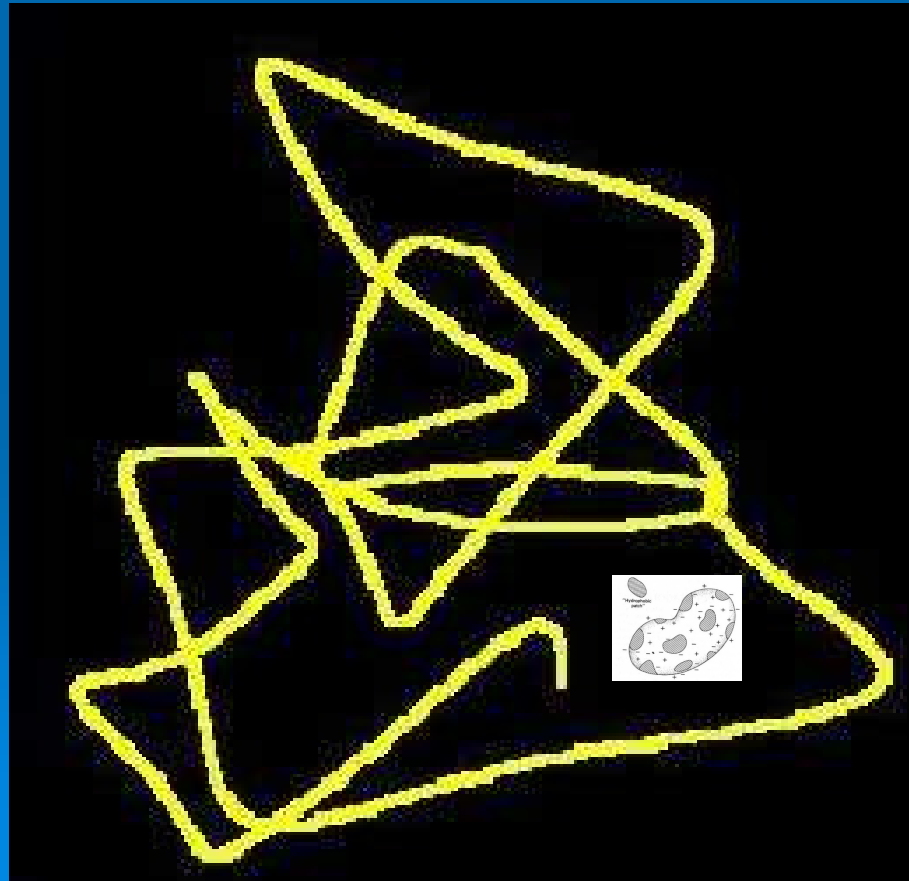


Efficacy – Crescent Innovations' Thoughts

- *Hyaluronic Acid, and Poly-g-glutamic acid*



Efficacy – Crescent Innovations' Thoughts



Efficacy – Crescent Innovations' Thoughts

- ***gPGA***

- Neg. charge per glutamic acid (MW=128)

- ***HA***

- Neg. Charge per disaccharide (MW=360)

- ***gPGA HAS TRIPLE CHARGE DENSITY***

Status

- ***Completed “Behavioral Modification Study”***
- ***Preparing for Clinical Trials***



Questions

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