Non-Confidential Joint/Bone/Skin

Crescent Innovations Technologies

1. 7,501,396: Methods for treating joint pain using poly-gamma-glutamic acid.

Abstract: *Methods for treating joint pain such as temporomandibular joint disorders, osteoarthritis of the knee, hip and other types of inflammatory joint diseases. The methods involve the use of poly-gamma-glutamic acid.*

Date of Issue: *March 10, 2009*

2. 9,603,855: Injectable osteogenic formula and method of using same.

Abstract: *Formulations and methods for growing hone in a site specific location using an osteogenic molecule such as a prostaglandin, and a delivery vehicle which is preferably a polymer matrix.*

Date of Issue: *March 28, 2017*

3. 7,371,399: Polymer gel containing hyaluronic acid and collagen, and its use in joints.

Abstract: *Formulations and methods for treating joints, such as temporomandibular joint disorders, osteoarthritis of the knee, hip and other types of inflammatory joint diseases. The method involves identifying specific matrix metalloproteinases (MMPs) that may be responsible for degrading the soft tissues of the joint in question, identifying the specific component of the joint the MMP(s) are targeting, and injecting a polymer gel with the component the MMP(s) seek to destroy, thus preserving the joint and allowing time to heal. These formulations typically require a mixture of glycosoaminoglycans and collagen proteins. One formulation in particular includes both hyaluronic acid and at least type I collagen.*

Date of Issue: *May 13, 2008*

All Previous Patents Supported by a "manufacturing" Patent:

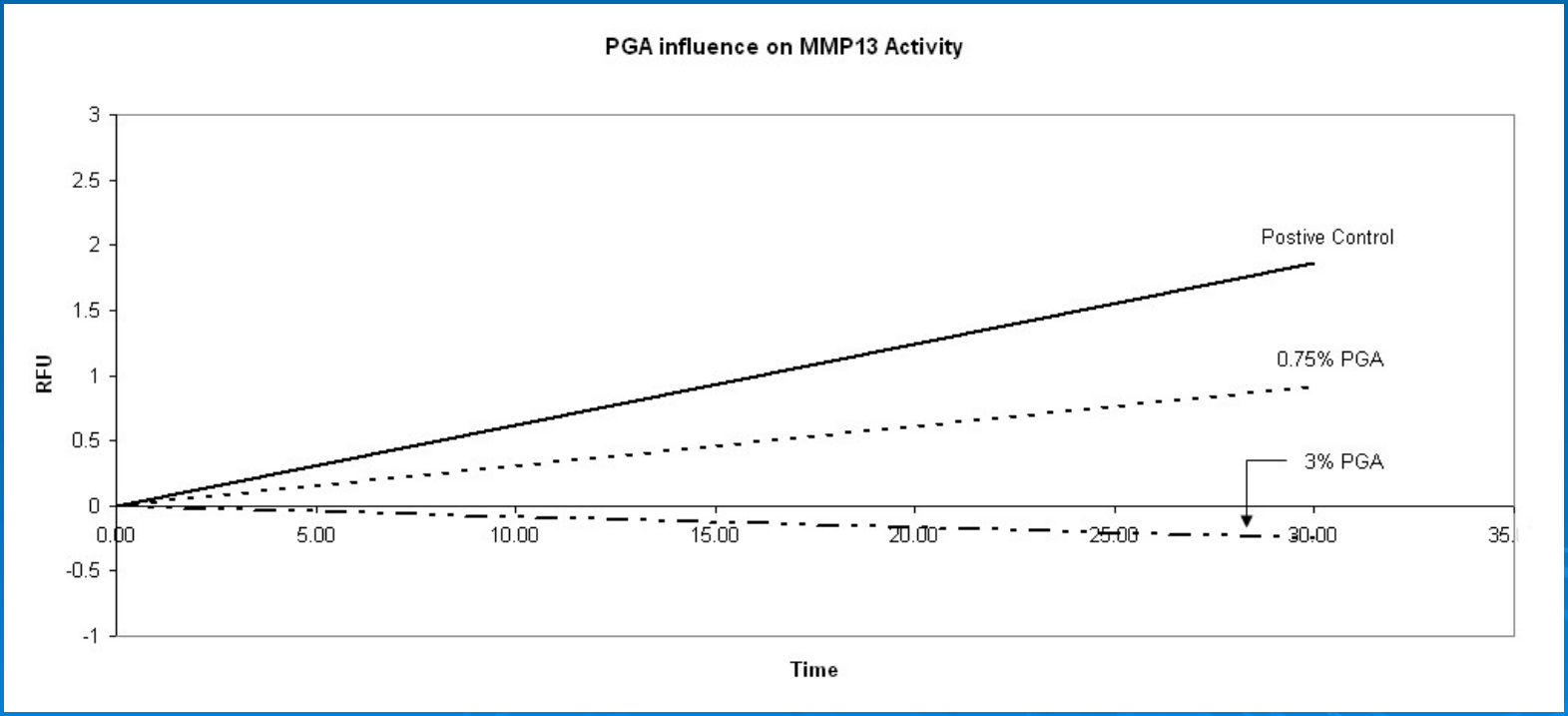
7,364,875: Method for producing medical and commercial grade poly-gamma-glutamic acid of high molecular weight.

Abstract: *Methods for producing high molecular weight poly-gamma-glutamic acid (PGA). The PGA is produced by fermentation, and purified by use of tangential flow filtration, followed by diafiltration, as necessary, to yield a product of the desired purity. Product obtained may be of very high purity using all the prescribed purification steps. Product of this purity is suitable for in vivo medical applications. Other applications, such as food or agricultural, may utilize lower purity levels, and hence do not require all the purification steps specified.*

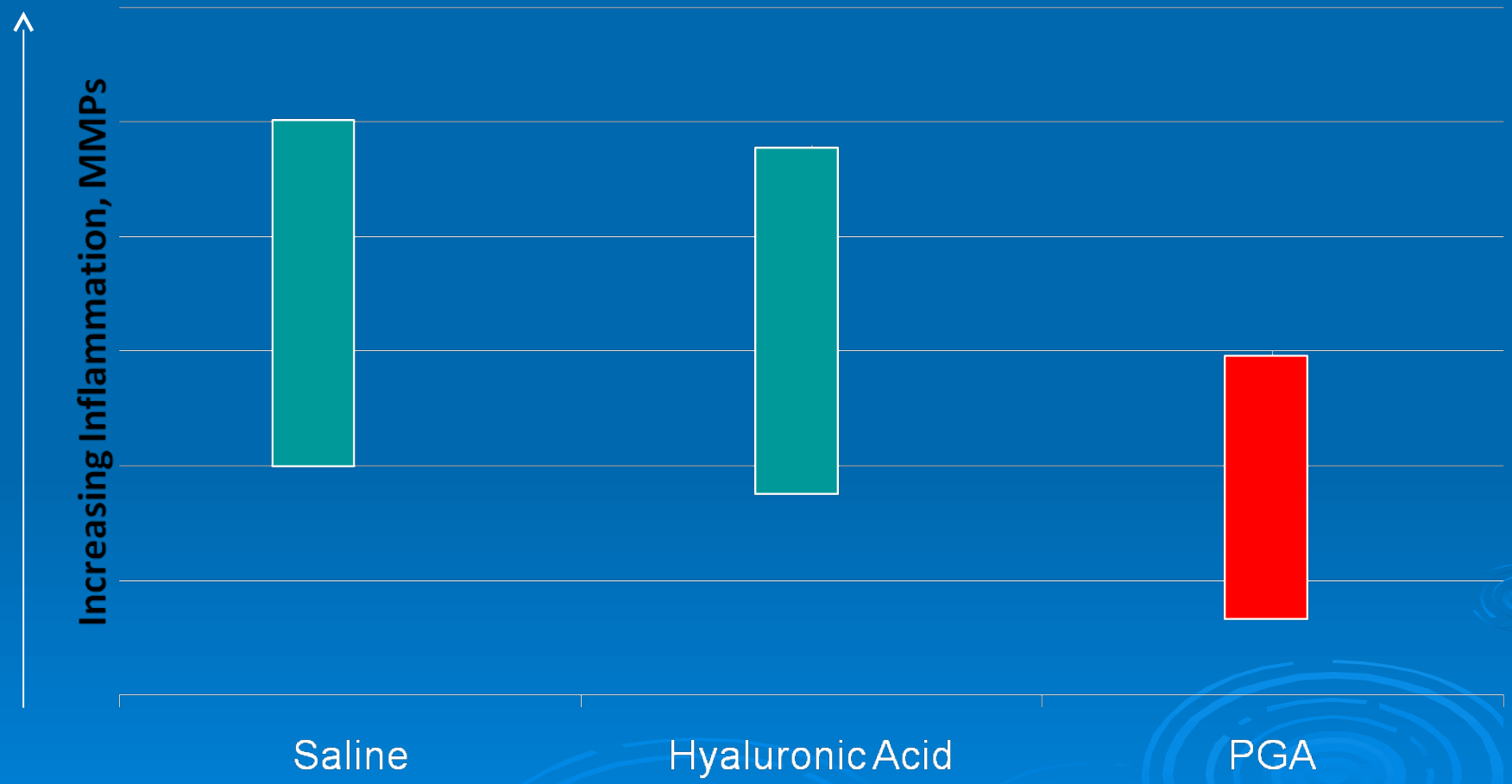
Date of Issue: *April 29, 2008*

Patent 7,501,396: Treating joint pain using Pg GA

Initial data for patent was in nitro collagen MMP activity data:



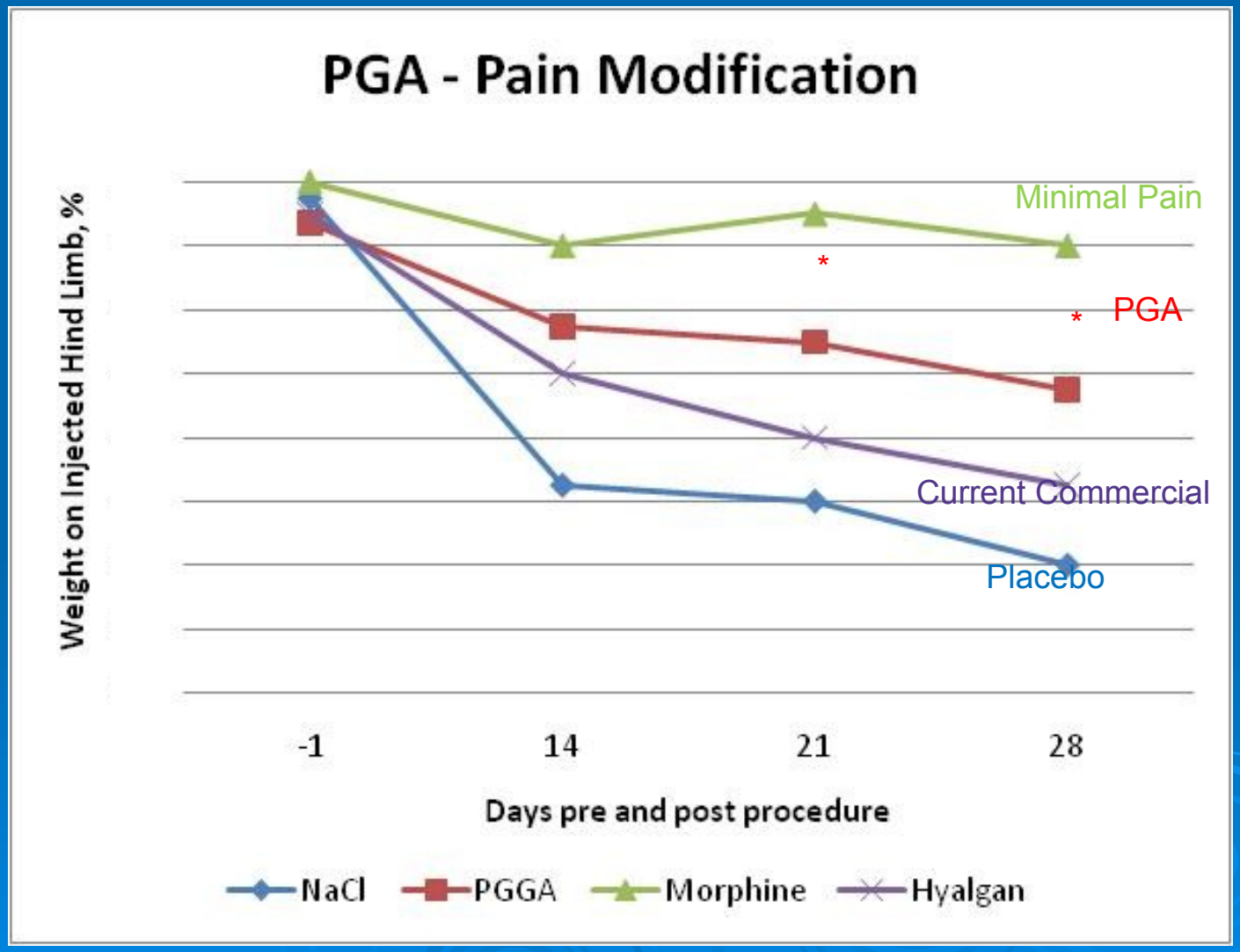
Later, in viva Inflammation in a rat model was obtained showing PGA superior to current state of the art, HA (REDACTED)



Slide 5

Certain parts of this graph have been redacted for confidential reasons

Finally, in vivo Pain Control Data was obtained (REDACTED)



Certain parts of this graph have been redacted for confidential reasons

PGA Pre-Clinical Safety Data

Test	Result	
Cytotoxicity	**PASS**	Mammalian Cells
Sensitization / Irritation	**PASS**	Guinea Pigs
Intracutaneous Direct	**PASS**	Rabbit
Systemic Toxicity	**PASS**	Mice
Rabbit Pyrogen	**PASS**	Rabbit
Genotoxicity	**PASS**	Salmonella Typhimurium, and E. Coli
Hemocompatability	**PASS**	Rabbit
Hemeolysis	**PASS**	Rabbit
Implantation	**PASS**	Rabbit

Patent 9,603,855: Injectable osteogenic formula and method of using same. LEAD

Initial data for patent was for Prostaglandin E1 (PGE1) in PgGA.

Continuation in Part (CIP) was received for HA as well.

LEAD – Introduction

LEAD is a combination of prostaglandin E1 (PGE1) and a delivery polymer. It is delivered in hydrogel format to the specific site of the bone defect. PGE1 is released as the polymer is resorbed.

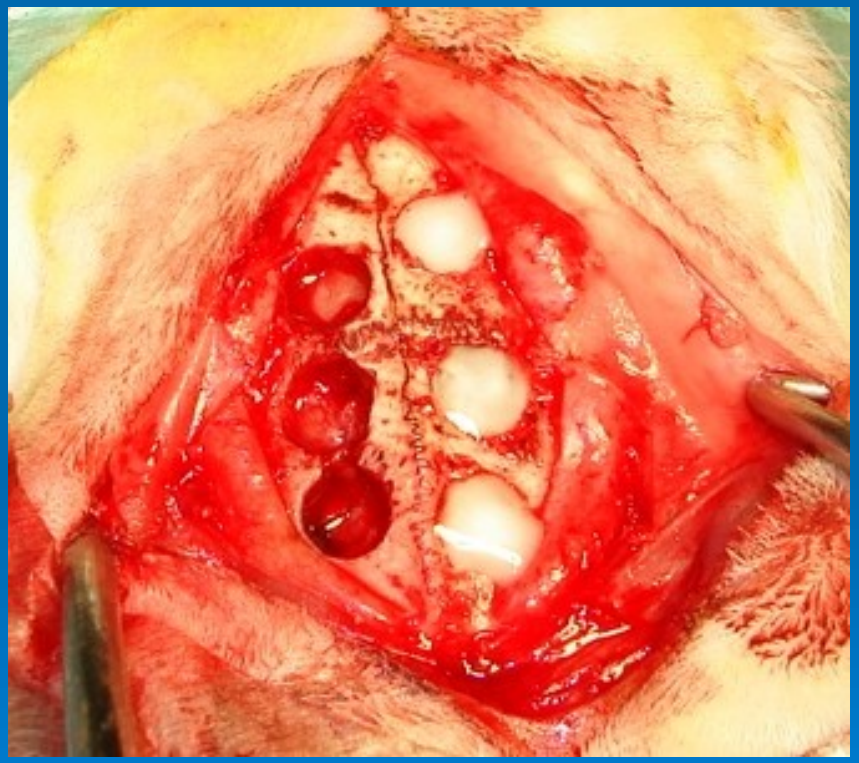
US Patent 9,603,855 for this technology has been issued, and a CIP for additional claims has been submitted

LEAD – Test #1

Two 5 MM burr holes were created in a Rabbit Cranial Model. 3 were left untreated, and 3 were treated with LEAD.

Test was run for 6 weeks and terminated.

LEAD – Test 1



LEAD can be seen on the right side as a while gel. The goal is for it to be injectable.

6 Weeks later, the test was terminated, and bone was examined by histology

LEAD – Test 1 (Redacted)

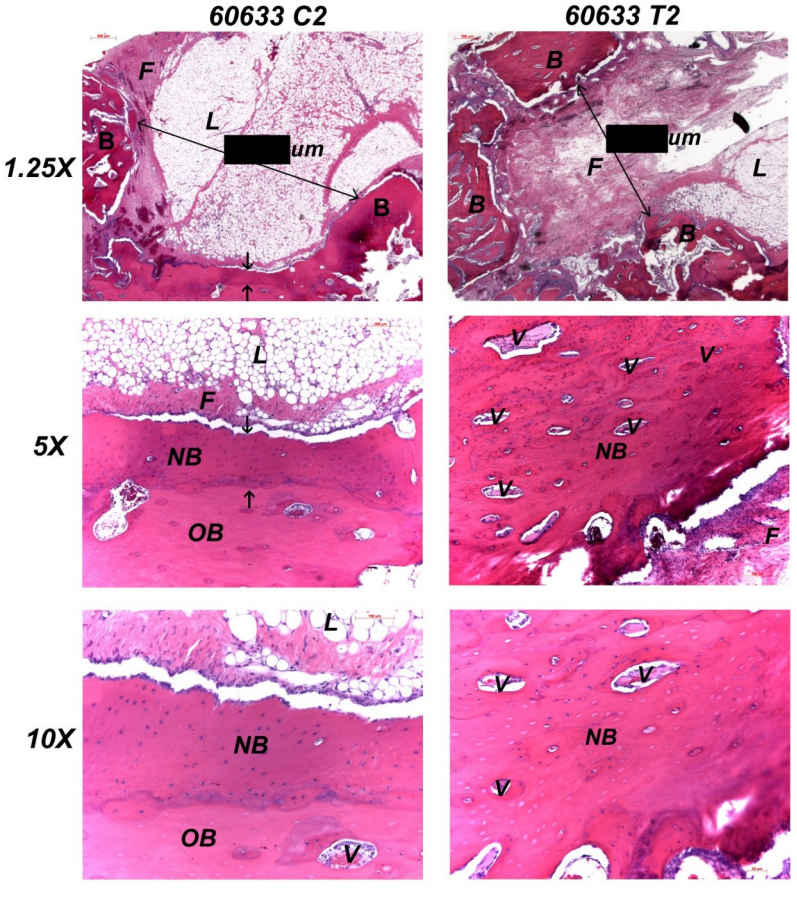
CONCLUSION

The test article was implanted in the bone of albino rabbits for a period of 6 weeks. The results indicated that the test article does not demonstrate any remarkable toxicity difference when implanted for 6 weeks (Bioreactivity Rating of 0.7) when compared to the untreated control sites. The test material appeared to increase bone growth in a possible dose dependent manner.

Control site.
Healed to x.x mm.
(Defect was 5mm)

F = fibrous material
NB = New Bone
OB = Old Bone

NB is very dense without any vascularization.



Test site.
Healed to x.x mm

NB = New Bone
NB is highly vascularized and still growing

NB blood vessels still numerous.

LEAD – Test 2

Test #1 repeated with original prototype, and a newer prototype utilizing a chemically bound PGE1/polymer.

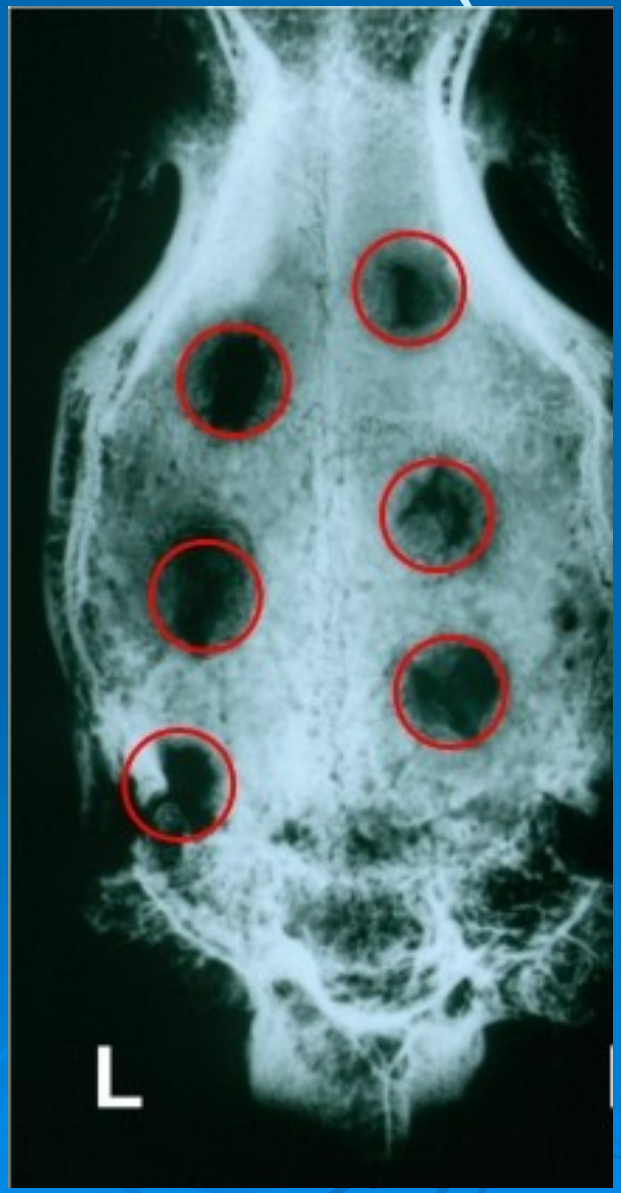
LEAD – Test 2 (Redacted)

LEAD Formula #1
Red circle site of defect.
(5 mm)

In growth to x.x mm

In growth to x.x mm

Defect not used due to Damage.



LEAD Formula #2
Red circle site of defect.
(5 mm)

In growth to x.x mm

In growth connected with x.x mm gaps

In growth connected with one x.x mm gap and one x.x mm gap

7,371,399: Polymer gel containing hyaluronic acid and collagen, and its use in joints.

Patent originally developed for Crescent's TMJ Disorder therapy, NINJA™

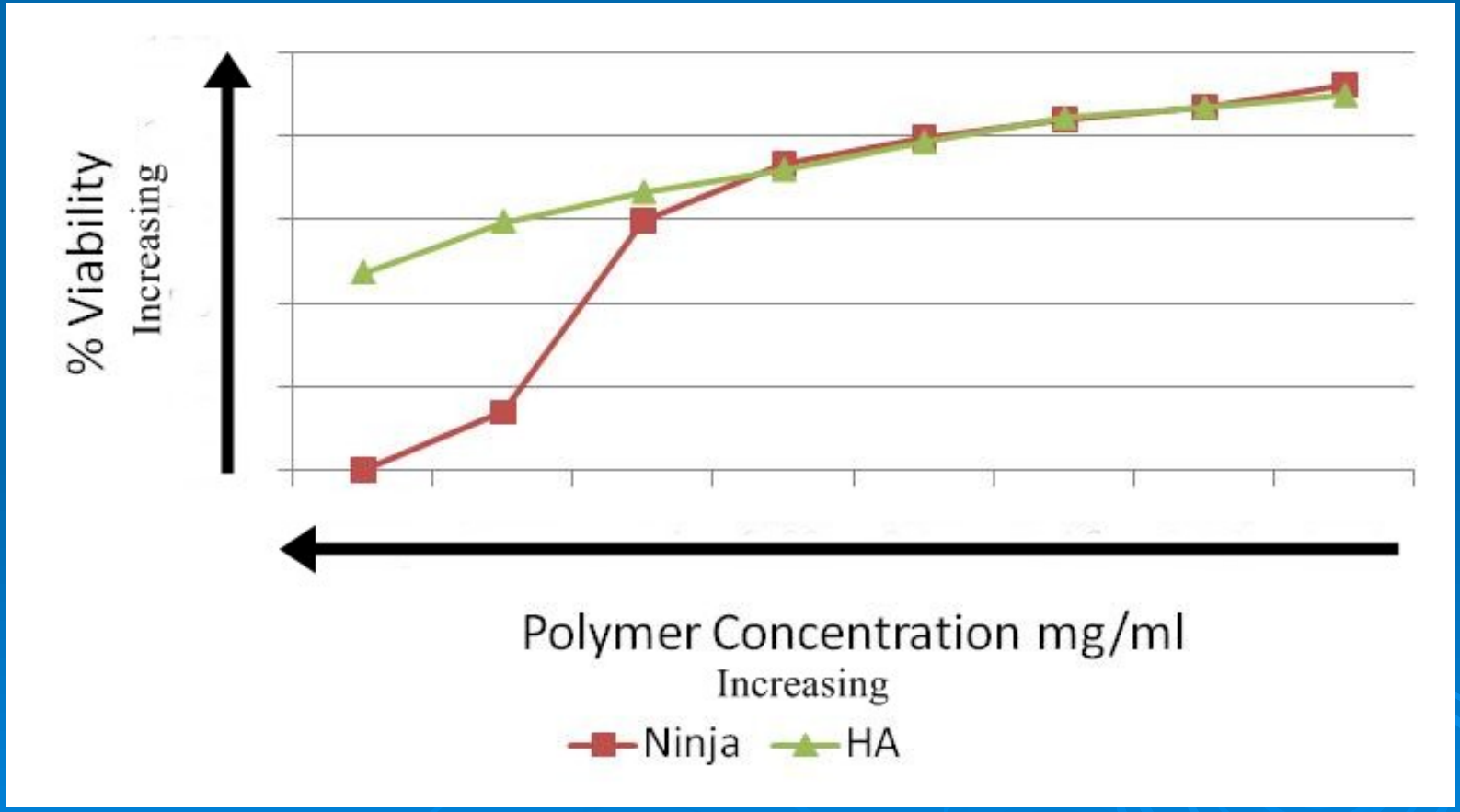
Further work showed that it was an enabling technology for autologous skin cell treatments for skin wounds

Application would be, biopsy a person, trypsinized and isolate keratinocytes, load into hydrogel, and deliver to wound.

Test #1: Verify cell viability

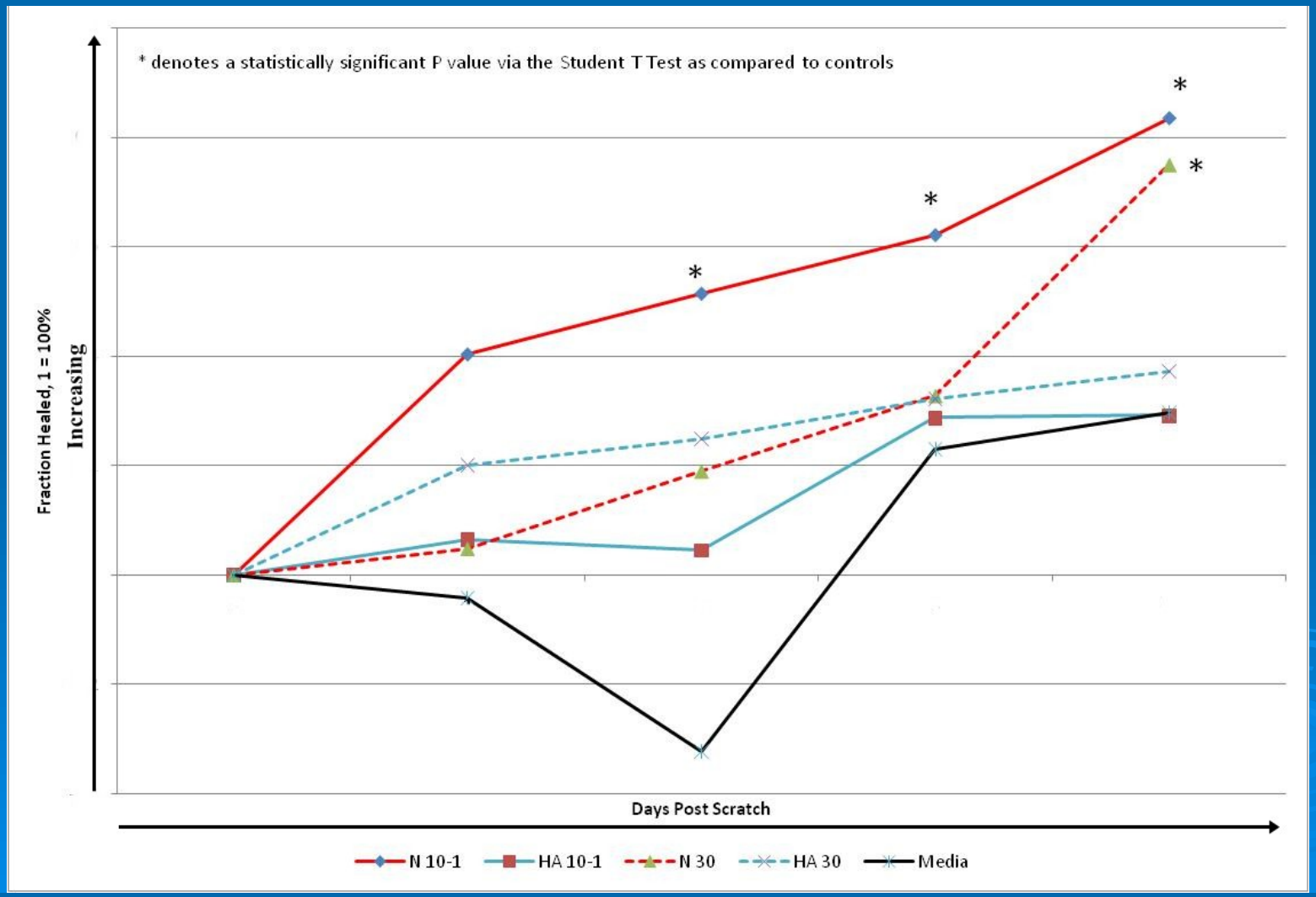
Test #2: Test simulated healing in a in vitro wound model.

Test #1: Cell Viability (Redacted)



Reduction in Cell Viability at concentrations above xxx ug/ml is likely due to viscosity of the hydrogels reducing nutrient diffusion to cells. This is supported by the added decrease in viability seen in the NINJA hydrogel at concentrations greater that x.xx mg/ml. NINJA is more viscous at equivalent polymer concentrations than HA.

Test #2: *in vitro* Scratch Assay (Redacted)



Questions

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