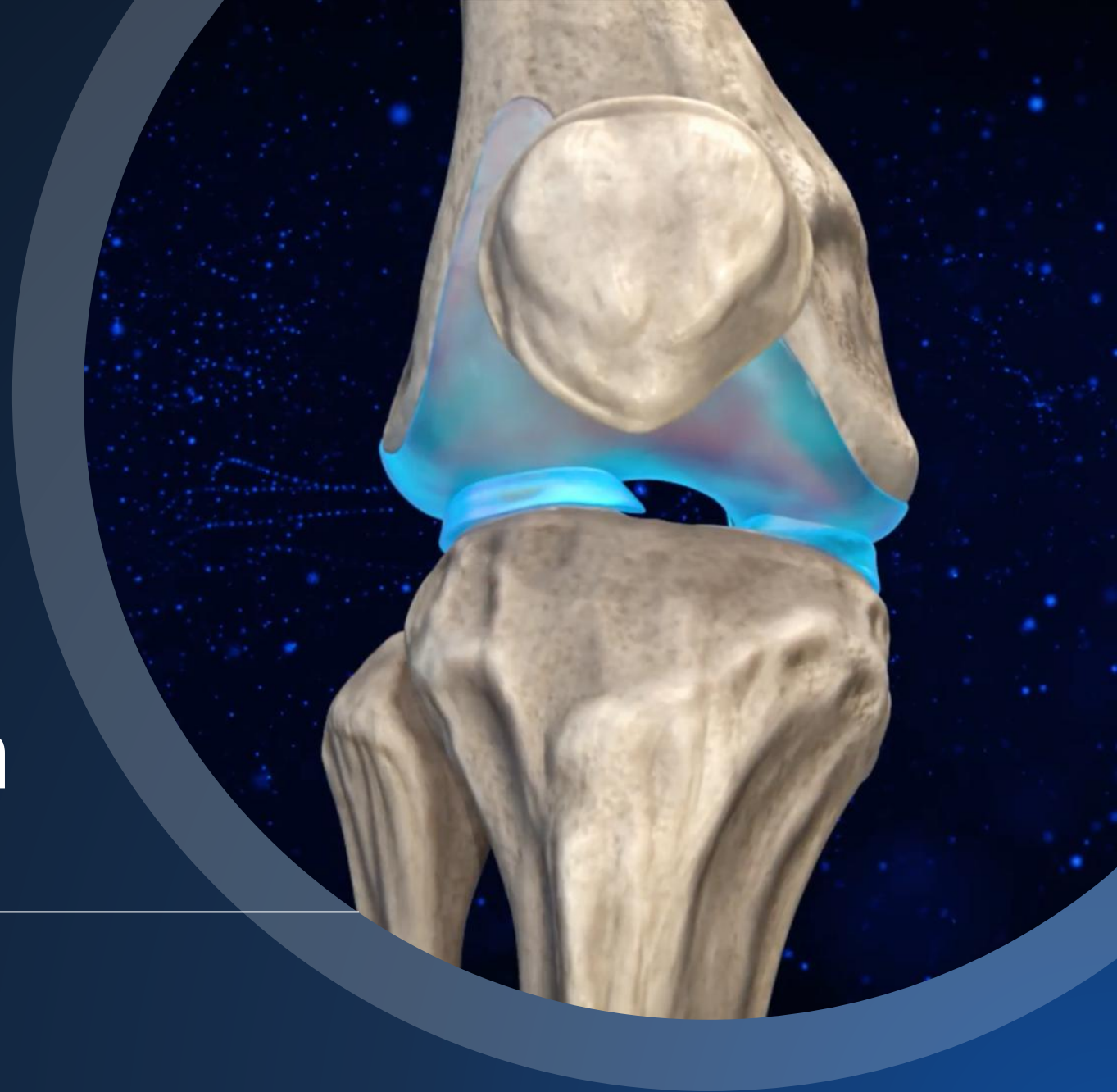




Engineering the Future of Joint Health with Molecular Precision

Join us in a *grassroots* effort to reclaim biotech
innovation from Big Pharma and Wall Street



Reg CF Disclaimer

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The information included herein is provided for illustrative purposes only to reflect Management's beliefs regarding certain market dynamics based on its research and analysis. Although Management considers such beliefs reasonable, they are based on criteria that are inherently subjective and rely on assumptions that may ultimately prove incorrect. The information included herein is subject to change, even materially, without notice and should not be construed as business, investment, tax, accounting or legal advice. Nothing herein should be construed to imply that any current or future business plans will be profitable or successful in executing on its business strategy. Nothing herein constitutes an offer to sell or solicitation of an offer to buy investment interests in any current or future securities being offered by the Company. See "Important Information" at the end of this presentation for additional details.

*“He who has a **Why** can endure any **How**”*

~ Friedrich Nietzsche

The **What**

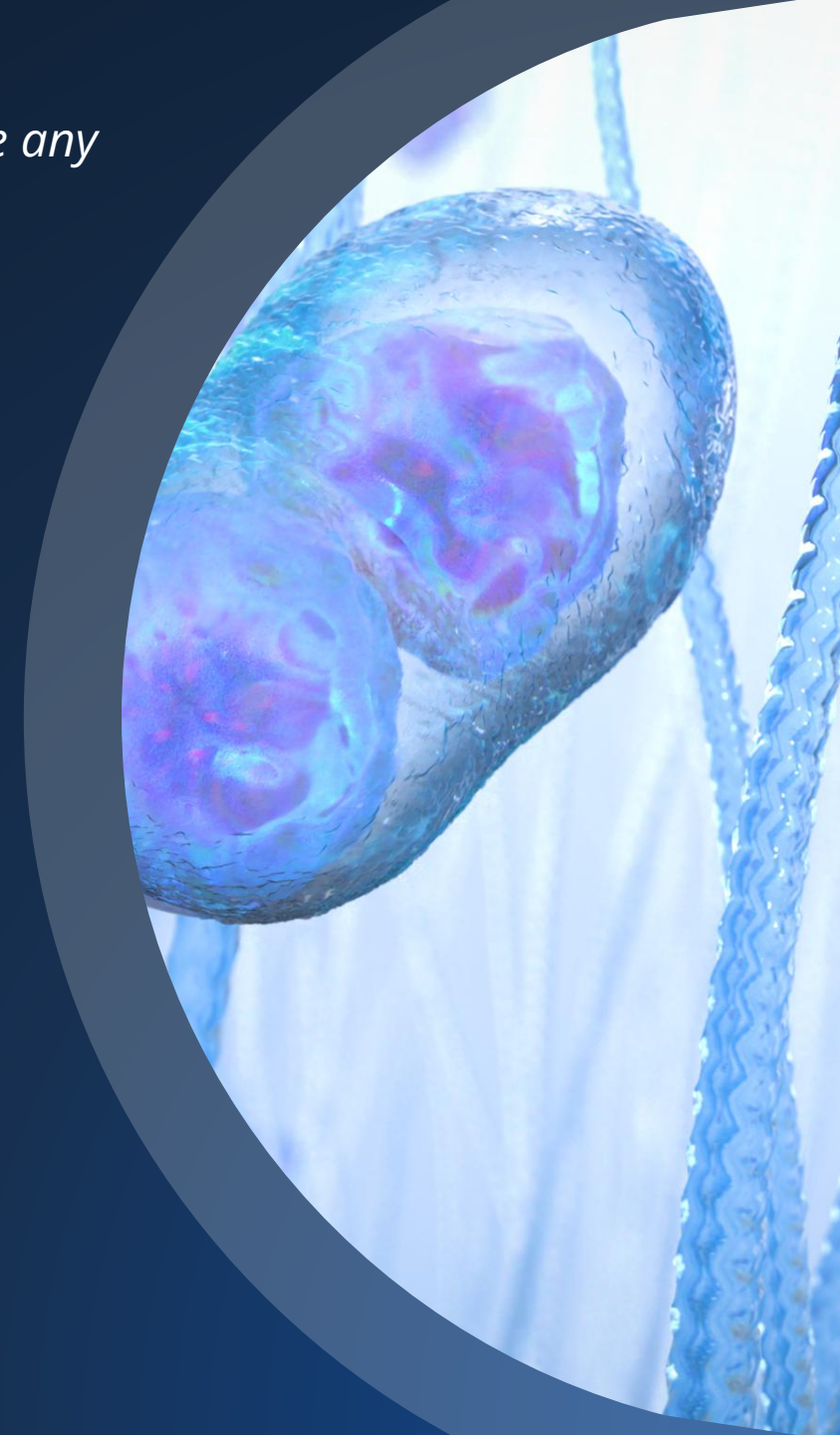
We are on a mission to develop the *first* **disease-modifying** therapy for OA, solving a problem Big Pharma has not been able to crack for decades

The **Why**

Osteoarthritis is currently a life sentence of pain and debilitated quality of life due to Big Pharma's failure. This is simply not acceptable.

The **How**

We are positioning ourselves to succeed where Beat Big Pharma has failed by addressing their *myopic* approach to drug development. In doing so, we will reclaim biotech innovation from Silicon Valley and Wall Street's stranglehold



The Osteoarthritis Epidemic

Osteoarthritis (OA) is a progressive joint disease where cartilage breaks down, leading to pain, stiffness, and reduced mobility. Unlike a single-cause illness, OA is driven by multiple enzymes that degrade cartilage, leaving joints stiff and painful.



◀ **currently suffering** from OA in the **USA***
This figure is projected to reach **25%** of the adult population by **2030**.



◀ **Global prevalence****
Agnostic to wealth or standard of living
Post-traumatic or chronic condition
Affecting both athletes and the elderly



\$1.1T burden to the **global economy*****

*<https://oaaction.unc.edu/oa-module/oa-prevalence-and-burden>

** <https://www.who.int/news-room/fact-sheets/detail/osteoarthritis>

*** <https://www.sciencedirect.com/science/article/pii/S106345842100738X>

The **Root Cause** of OA

OA is caused by **hyperactive proteases**, a class of catabolic enzymes that degrade cartilage tissue.

A successful **disease-modifying OA drug** (DMOAD) must address target these protease enzymes. It restore joint health by encouraging tissue repair, reduce pain, and ultimately improve long-term quality of life.



Current OA Treatments are **Failing**

Current OA treatments relieve symptoms but don't address the root cause.

Conventional therapies are palliative, masking joint pain and inflammation temporarily, but fail to address the root molecular cause of the disease.



Non-steroidal Anti-inflammatory Drugs

(e.g., Advil)



Temporary inflammation and pain reduction



Hyaluronic Acid

(viscous supplementation)



Temporary artificial cushioning



Corticosteroids

(e.g., Prednisone)



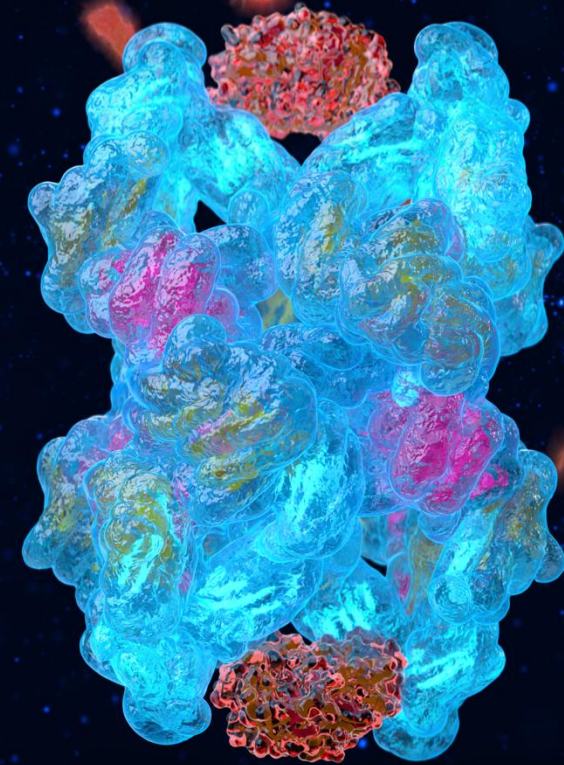
Temporary inflammation reduction, many side effects of chronic use

Our Solution:

CYT-108: The First Disease-Modifying Therapy for Osteoarthritis

**A Precision-Engineered “Super”
Alpha-2-Macroglobulin (A2M) that
Targets OA at its Root Cause**

- Protease inhibitor with potent inhibitory activity against the proteases that are upregulated in OA
- Targets OA at its root cause to protect cartilage damage and the joint membrane
- Highly concentrated for targeted delivery directly into joint space
- Preclinical studies demonstrate significant reduction in the progression of OA
- Capable of manufacturing at scale and global distribution as a shelf-stable compound



“Nature’s Blueprint, Perfected.”

How CYT-108 Works

A2M is a naturally-occurring protease inhibitor that protects against cartilage degradation. Though levels are too low in joints to be an effective treatment...

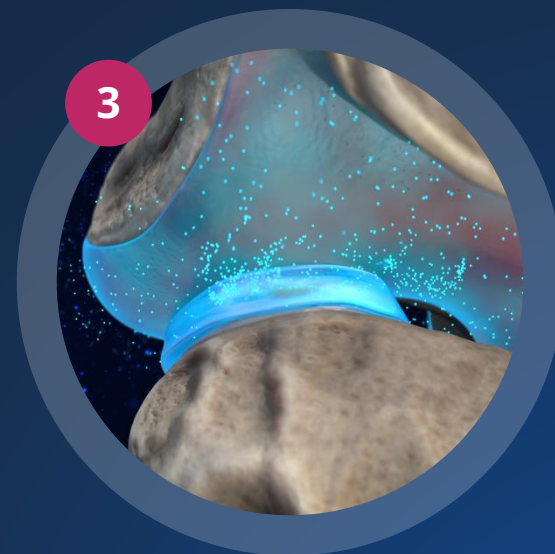
CYT-108 is a genetically engineered “**super**” **A2M**” protein that is **200%** more potent than the naturally-occurring A2M.



1
Intra-articular (targeted) delivery for maximum concentration and minimum off-target effects



2
Sequesters cytokines and neutralizes destructive proteases, cutting off the inflammatory feedback loop

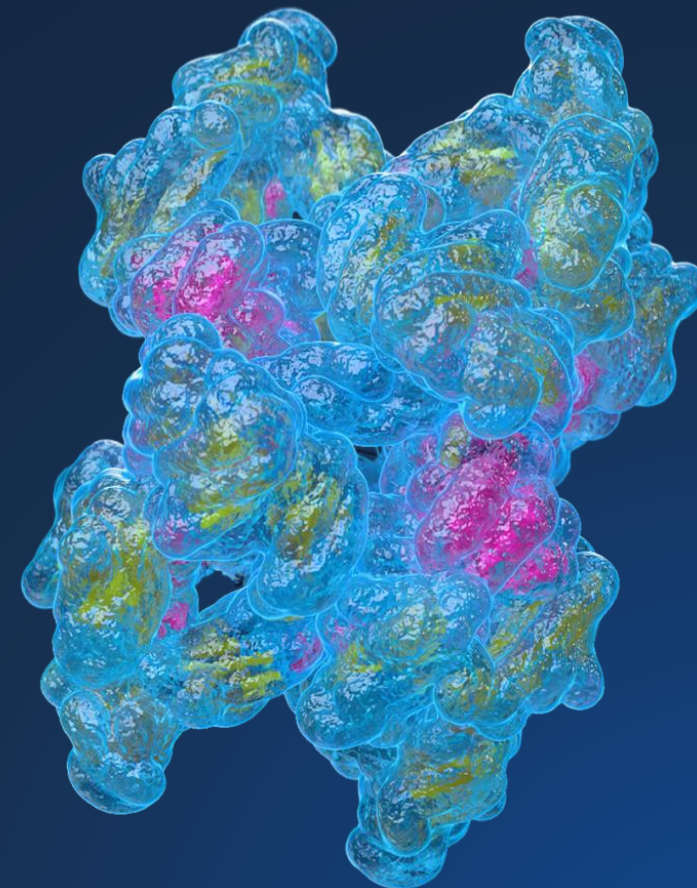


3
Designed to quickly reduce joint pain and inflammation while halting progressive cartilage degradation

Leveraging Nature's Beautiful Design

*the power of **Alpha-2-Macroglobulin (A2M)***

- **Alpha-2-Macroglobulin (A2M)** is a blood serum protein that plays a role in the clotting cascade.
- A2M is a *very* well characterized, broad-spectrum **protease inhibitor** that has demonstrated potent inhibitory activity against the proteases that are **upregulated** in OA.
- A2M's two "*bait regions*" act as a **Venus Flytrap** for proteases, encapsulating and rendering them inactive.
- Unfortunately, the **naturally occurring levels of A2M are too low** to lend any therapeutic benefit to damaged joints.
- We theorized that delivering **high concentrations of A2M** directly **into the joint space** could bind to and inhibit the proteases, slowing and eventually **halting the progression of OA**.



See Appendix for supporting A2M efficacy data and related scientific publications

*Now, we just had to **prove it**.*

Harnessing the Power of Alpha-2-Macroglobulin (A2M)

Our first-generation technology, the **Autologous Protease Inhibitor Concentrate (APIC™)** therapy put A2M on the map.

- The **APIC™** therapy selectively concentrates A2M from a patient's *own blood* to treat OA.
- **Successfully treated over 10,000 patients nationwide**, providing clinical and commercial proof of the therapeutic potential of the A2M protein. *See testimonials in Appendix.*
- Limitations: patient-to-patient variability in A2M levels, requires equipment and training, A2M extraction ~2hrs, insurance coverage



*What if we don't have to rely on **natural** A2M...?*

APIC™ Blood Processing & A2M Extraction



Blood is drawn from the patient (50-100mL)



The blood is injected into a 50mL falcon tube...



... and placed in a centrifuge



The centrifugation process separates the plasma (containing A2M) and red blood cells



The plasma is injected into the proprietary APIC™ tangential flow filtration system

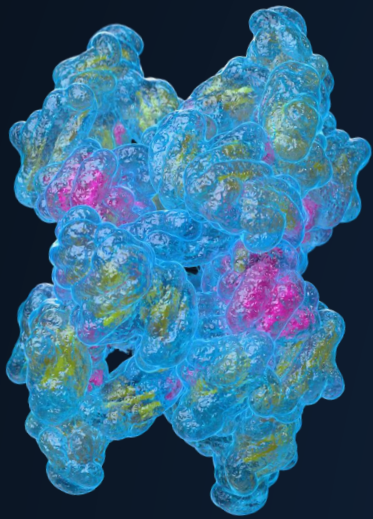


The A2M-rich concentrate is withdrawn from the APIC™ "collection" reservoir and injected directly into the patient's joint(s)

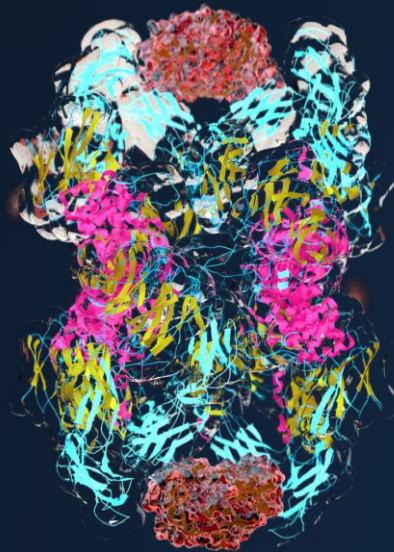
From APIC™ to CYT-108

The next generation of A2M therapy

Cytonics has genetically engineered a **“super A2M”** designed to specifically target and efficiently eliminate **ALL major classes proteases** involved in OA.



Natural A2M:
APIC purified from
patient blood



CYT-108: genetically-
engineered
(recombinant) A2M

	APIC™	CYT-108
Source	Patient's own blood	Genetically-engineered (recombinant A2M)
Efficacy	Patient-to-patient variability	Precisely dosed, 200% more potent & optimized against MMP-13 and ADAMTS-5
Scalability	Limited by blood processing	Laboratory production
Insurance Coverage	Uncertain	High potential

Nature's Blueprint, Perfected



APIC™
validated A2M's
effectiveness



CYT-108
*is Nature's Blueprint,
Perfected*



APIC™
is limited by
patient-derived A2M



CYT-108
is scalable, shelf-stable,
and mass-producible for
global distribution



APIC™
was a great first step



CYT-108
is the future of
OA treatment, high-
probability of becoming
1st line therapy

CYT-108 is Non-Toxic and Safe to Administer

Preclinical Safety Results



ORGAN PATHOLOGY

Does administration of CYT-108 affect the health of major organs?

"...pathology revealed findings consistent with those commonly observed in laboratory subjects, and not in laboratory subjects, and **[no organ damage was] attributed to treatment with CYT-108.**"

NO ORGAN DAMAGE



IMMUNOGENICITY

Does administration of CYT-108 **induce antibody creation?**

Anti-CYT-108 antibodies are created within 1 week of administration, and rapidly clear out "excess" CYT-108 that leaks into the bloodstream. These antibodies remain active over time. No additional CYT-108 was detected in the bloodstream upon subsequent injection, **indicating a rapid and robust clearance without adverse effect on the animal.**

IMMUNE CLEARANCE

CYT-108 Protects Cartilage and Joint Tissue

Preclinical Efficacy Results

CYT-108 has therapeutic effect in protecting articular cartilage, bone, and synovial membrane physiology when administered to subjects suffering from post-traumatic osteoarthritis, and substantially restores the cartilage matrix, underlying subchondral bone, and the synovial membrane back to normal, healthy anatomy and physiology.

Recovery of
~57%
of the damage to the
cartilage structure
as measured by Safranin-O staining

Restoration of
~46%
of the damage to
chondrocytes
(cartilage-secreting cells)

Enhancement of
~10%
proteoglycan content
(key component of cartilage)

Reduction of
~77%
of the subchondral
bone plate thickness
back to normal levels

Reduction of
~60%
of the pathological
accumulation of cell
layers in the synovial
membrane

Reduction of
~31%
of the synovial tissue
hyperplasia back to
normal levels
(pathological membrane
thickening)

See Appendix for supplemental CYT-108 efficacy data

CYT-108 Phase 1 Clinical Study

As a true “disease-modifying” treatment, CYT-108 will catalyze a new era of quality of life, enabling everyone to enjoy an active, pain-free existence into their golden years.

If approved by the FDA, CYT-108 will likely be the first and only biopharmaceutical capable of targeting OA's root cause, providing *both symptomatic relief and restoring the joint to a healthy state.*

APRIL 2025

First-in-human trial for CYT-108 concluded

OCT 2025

Database locked; statistical analysis underway

Q1 2026

Clinical Study Report

Savings up to

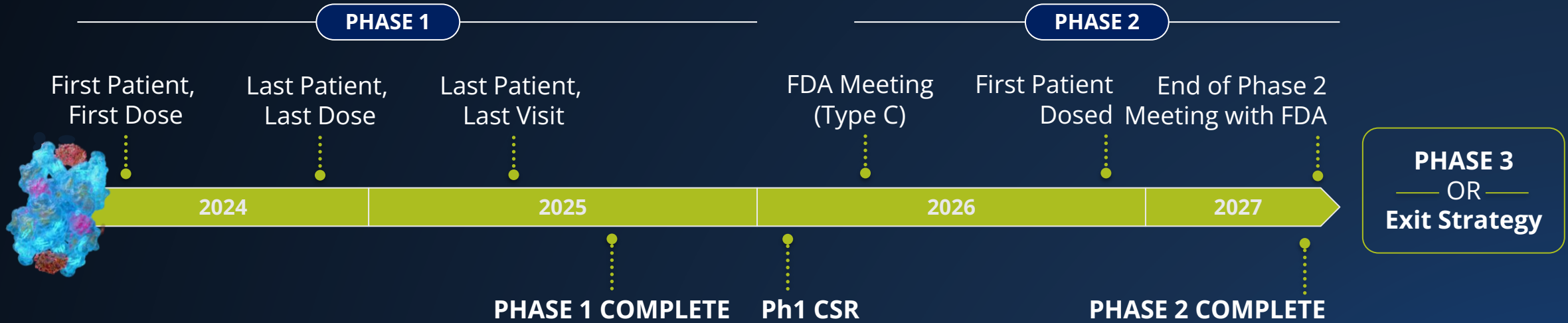
\$27B
annually*

Attractive to Insurance Payers

If approved, CYT-108 will be an **attractive first-line therapy** due to its ability to **obviate joint replacement surgeries**, as a biopharmaceutical that has demonstrable efficacy in randomized clinical trials, can be synthesized on an industrial scale and distributed globally.

Avg cost of U.S. Total Knee Replacement:
\$33,000

The Path to CYT-108 Approval



PHASE 3 SCENARIO:

- Initiate Phase 3 **4Q '27**
- Phase 3 concludes **4Q '28**
- Biologic License Application submitted to FDA for possible approval **1Q '29**

POTENTIAL EXIT SCENARIOS:

IPO

- **Raise capital** for PHASE 3
- Uplist to **NASDAQ**
- Stock becomes **liquid** (buy/sell)

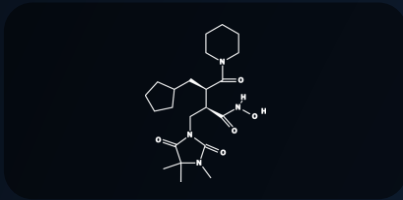
ACQUISITION

- Acquirer buys **PHASE 2 asset**
- All shareholders bought out in **private deal**

STRATEGIC

- **PHASE 2 "BioBucks"**: upfront cash, milestones, and royalties
- Decision: IPO *or* remain private → dividend? Use cash to fund new R&D?

Succeeding where **Big Pharma** has failed



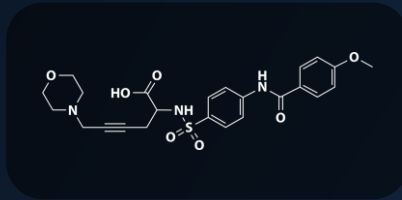
Cipemastat (Trocade)

Manufacturer:
Roche

Date of Failure:
~2001

Reason:
**Lack of efficacy;
musculoskeletal side
effects due to off-target
toxicity**

CYT-108 broadly inhibits multiple protease classes simultaneously and closely mimics a natural human protein, ensuring safety and tolerability even at supraphysiological levels due to its endogenous origin



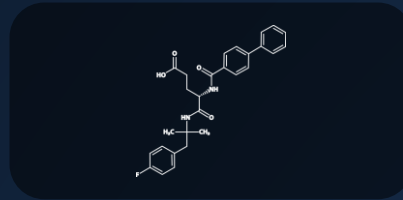
PG-116800

Manufacturer:
Proctor & Gamble

Date of Failure:
2004

Reason:
**No efficacy; severe
musculoskeletal toxicity
(shoulder pain, tendon
fibrosis)**

CYT-108 has proven safety in preclinical studies at doses up to 10x intra-articular concentrations, indicating significantly reduced risk of musculoskeletal adverse events compared to traditional synthetic inhibitors



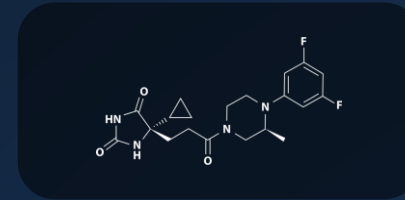
AGG-523

Manufacturer:
Wyeth (Pfizer)

Date of Failure:
~2009

Reason:
**Terminated early due
to strategic
reprioritization; no
established efficacy
signal**

CYT-108's development is substantially de-risked because its effectiveness is supported by both robust *in vivo* animal data and commercial success of natural A2M in APIC™ therapy



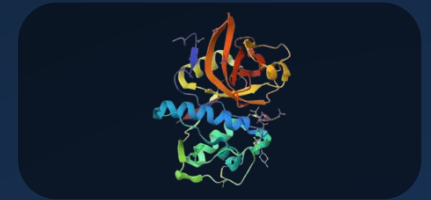
GLPG1972 (S201086)

Manufacturer:
Galapagos NV/Servier

Date of Failure:
2020

Reason:
**Lack of structural and
symptomatic efficacy;
failed primary endpoint
of cartilage preservation.**

CYT-108 has been shown to restore joint tissues (cartilage, synovial membrane, bone) back to healthy states *in vivo*. It also positively influenced anabolic metabolism markers, providing evidence of potential clinical symptomatic relief and disease-modifying effects



MIV-711

Manufacturer:
Medivir AB

Date of Failure:
2019

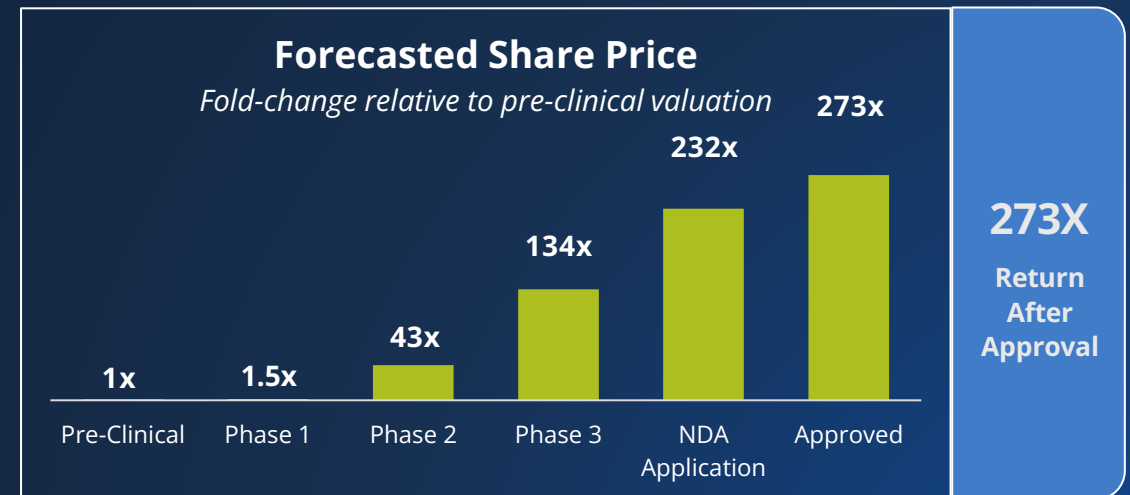
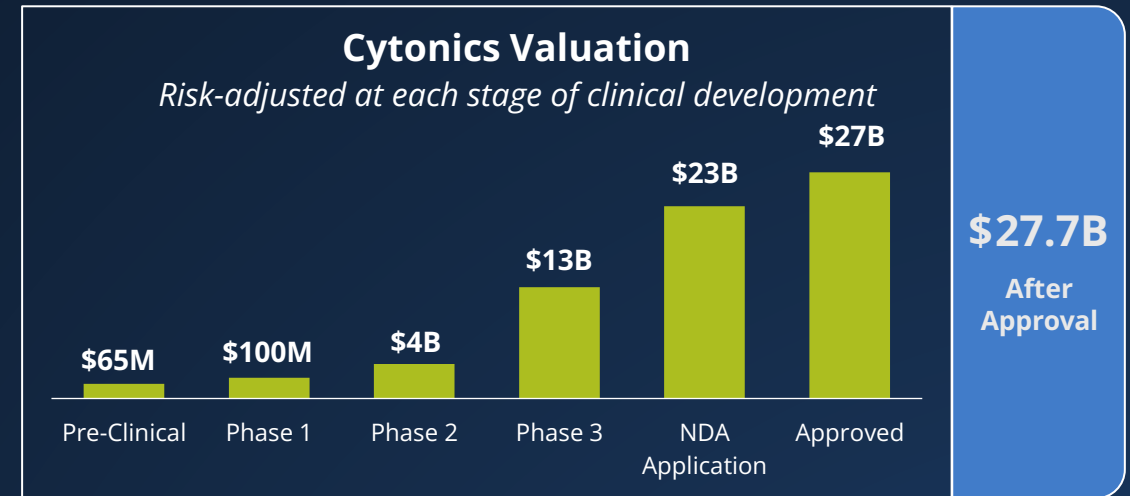
Reason:
**Structural efficacy
without symptomatic
improvement**

CYT-108 has demonstrated *both* cartilage preservation and significant anabolic activity, suggesting likely disease-modifying improvements as well as symptomatic relief. It addresses patient pain and mobility which are clinically meaningful endpoints that MIV-711 failed to meet

Let's talk Growth increasing shareholder value

Risk-Adjusted Discounted Cash Flow Assumptions:

- **Discount rate of 50%**
(this is appropriate for pre-clinical stage biotech)*
- **20% market capture**
(conservative estimate) in the US human orthopedic market *only*
(does not include expansion into other markets)
- **\$2,000 per treatment, avg. 2 treatments per year**
(Hyaluronic injections cost >\$2,000 each)
- Cytonics assumes full development cost of bringing CYT-108 to market and producing and selling the drug upon FDA approval
 - COGS = 15% of revenue (According to a meta-analysis compiled in Biotech Forecasting & Valuation (2016)**. Data was retrieved from company 10-k filings.)
 - SG&A = 34% (According to an analysis of 35 small- and mid-cap drug companies in the NASDAQ Biotechnology Index in 2015, reported in Biotech Forecasting & Valuation (2016)**)
- Upon patent expiry, Cytonics loses 20% of CYT-108 sales per year (Terminal Value in perpetuity)



These figures are derived from a rDCF financial forecast and not guaranteed.

*<https://www.linkedin.com/pulse/valuation-methodologies-life-science-companies-crean-ph-d-mba/>

**David, Frank S, et al. "The Pharmagellan Guide to Biotech Forecasting and Valuation," Pharmagellan LLC, Pharmagellan, www.pharmagellan.com/book.

***Note: Increase in shareholder value calculated as the relative change in share price compared to the preclinical valuation, and accounts for future anticipated dilution to fund the Phase 2 and Phase 3 clinical trials.

These statements reflect management's current views based on information currently available and are subject to risks and uncertainties that could cause the company's actual results to differ materially. Investors are cautioned not to place undue reliance on these forward-looking statements as they are meant for illustrative purposes and they do not represent guarantees of future results, levels of activity, performance, or achievements, all of which cannot be made. Moreover, no person nor any other person or entity assumes responsibility for the accuracy and completeness of forward-looking statements, and is under no duty to update any such statements to conform them to actual results. Please see Data Room for additional detail regarding the assumptions underlying these projections.

A Half-Trillion Market Waiting for a Real Solution.

This debilitating disease must be stopped.

Over 500M people with OA have no access to an effective treatment that targets the disease at its source

OA affects 13X more people than Rheumatoid Arthritis (RA)

Global RA Sales:

(TNF- α inhibitors)

\$43 billion

13x

more people have **OA** than RA

Potential Global

OA Therapeutic Market:

\$560+ billion

OA prevalence: <https://www.who.int/news-room/fact-sheets/detail/osteoarthritis>

RA prevalence: <https://pubmed.ncbi.nlm.nih.gov/30285183/>

RA market size: <https://www.researchandmarkets.com/reports/5733874/tnf-alpha-inhibitors-global-market-report>

A Grassroots Effort: *For the People, By the People*

Biopharma

almost exclusively capitalized by Venture Capital.

Cytonics' CYT-108

program is exclusively funded by “everyday” investors, who have equipped us to take on Big Pharma and the Wall Street behemoths with the single cast of a stone.



Invest like a Venture Capitalist

- Private deal, pre-IPO / acquisition / strategic partnership
- High growth sector, biotech exit multiples



Challenge Big Pharma's stranglehold on innovation

- Big Pharma has failed to develop a disease-modifying therapy for OA, leaving patients with only palliative treatments
- Estimated ~ \$1B spent on failed clinical trials
- We know *why* they failed, and *what* to do about it



Subvert Wall Street's grip on the biotech sector

- Crowdfunding is *democratizing* biopharma investing
- Cytonics is backed by over 7,000 retail investors
- Disrupting the traditional VC funding model (and they are taking notice)

The Team

MANAGEMENT TEAM



Gaetano Scuderi, MD
Founder and Chief Medical Officer



Dr. Guy Scuderi is a Stanford-trained spine surgeon and pioneer in orthobiologics with decades of experience at the intersection of surgery and molecular medicine. His work led to the development of APIC, an A2M-based therapy that has treated over 10,000 patients, including professional athletes.

He founded Cytonics in 2006 with the vision of creating a scalable biologic form of A2M, resulting in CYT-108, and today leads the company's scientific and clinical strategy.



Joey Bose, MS
President & Chief Executive Officer



Joey Bose brings a unique combination of biomedical engineering, healthcare investment banking, and startup operating experience to the Cytonics team. Educated at Johns Hopkins and the University of Virginia, he began his career in biomedical research before advising emerging biotech companies on capital strategy and M&A.

Joey joined Cytonics in 2018 to help reimagine how breakthrough therapies are developed and funded, advancing the Company's development program from preclinical research through first-in-human clinical trials. Under his leadership, Cytonics has raised over \$25 million through equity crowdfunding and built a 7,000+ member investor base.

The Team

MANAGEMENT TEAM



Alan Liss, PhD

Head of Quality and Manufacturing



Alan Liss is a veteran GMP and regulatory leader with deep experience guiding biologics through global regulators. Trained as a microbiologist and immunologist, he has built quality systems, led inspection readiness, and supported INDs reviewed by the FDA, EMA, MHRA, and NMPA.

Previously, Alan helped establish Regulatory and Quality Affairs at BARDA and worked in the FDA Office of the Commissioner. At Cytonics, he brings disciplined GMP leadership to manufacturing CYT-108 from day one.



Michael Hartwich

Head of Creative Development



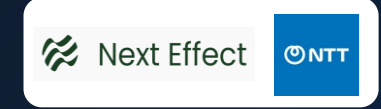
Michael Hartwich leads creative development and digital advertising at Cytonics, shaping how the company communicates its science, strategy, and long-term vision to investors and the public. His work focuses on translating complex biology into clear, disciplined narratives that build credibility over time.

With a background in visual storytelling and digital strategy, Michael has worked with early-stage and growth companies in highly regulated industries. At Cytonics, he oversees brand, campaign, and digital advertising efforts that support capital formation while maintaining scientific and regulatory integrity.



Alex Barton

Head of AI and Computational Biology



Alex Barton leads AI and Computational Biology at Cytonics, applying machine learning methods to develop our Foundational Osteoarthritis Clinical & Analytic Layer (FOCAL) model of OA disease pathophysiology and progression.

A lifelong technologist, Alex began building computers at age eight and joined a Washington, D.C.–based startup focused on national-security-grade encryption and biometric authentication before finishing high school. He later led offensive security operations at NTT Com Security and played a key role in scaling DigitalOcean from 5k to over 10k customers.

The Team

BOARD OF DIRECTORS



**Joey
Bose, MS**

President, CEO
and Director



**Gaetano
Scuderi, MD**

Founder, Chief Medical
Officer and Director



**Tracy
Goeken, MD**

Independent
Director



**Gordon
Ramseier, MBA**

Independent
Director



The OA Dream Team

MEDICAL ADVISORY BOARD



Ketan Desai, MD, PhD

Chief Medical Officer, Levolta Pharmaceuticals



Mark Schweitzer, MD

Vice President for Health Affairs, Wayne State University



Geoffrey D. Abrams, MD

Associate Professor of Orthopedic Surgery, Stanford University



Iain Lachlan (Lachy) McLean, MD, PhD

Chief Medical Officer, Genasence Corporation



Mukesh Ahuja, MD

Global Clinical Head of Osteoarthritis, Paradigm Biopharmaceutical

OUR COLLABORATORS



Self-Evident Success



Navigating FDA's regulatory process by commercializing APIC™ (510k clearance)



Proven tech with over 10,000 patients treated with APIC™ (first gen A2M therapy)
See Appendix



Awarded \$1.8M in NIH grants to pursue innovative treatments for osteoarthritis



\$32M+ in funding raised from family offices and equity crowdfunding (Reg A+/CF)



Over 7,000 equity crowdfunding shareholders invested over **\$25M**



De-risked development CYT-108 has demonstrated over **200%** more potency than the naturally occurring A2M utilized by FDA-cleared APIC™



Completed Phase 1 clinical study of CYT-108 as a treatment for osteoarthritis of the knee



A robust and multi-layered IP fortress of 25+ patent spanning key global markets (USA, EU, AU, JP, CA)
See Appendix

Join the Movement: Why Cytonics?

- ✔ Succeeding where Big Pharma has failed
- ✔ CYT-108 poised to be the *first* DMOAD ever created
- ✔ APIC™ uniquely de-risks development of CYT-108
- ✔ Track record of navigating FDA's complexity
- ✔ \$500B+ market potential for DMOAD drug
- ✔ Broad patent coverage in key geographies
- ✔ OA Dream Team: 5 MDs > 80 OA clinical trials
- ✔ No Corporate Backers, Just People on a Mission
- ✔ Uniting Individuals to Disrupt Big Pharma's Stranglehold

THE OFFERING

\$5M Reg CF Equity Crowdfund

USE OF FUNDS

OA Phase 2 Clinical Trials

Oncology pipeline expansion

EXIT STRATEGY

- Uplist to the NASDAQ
- Strategic Partnership
- Acquisition or BioBucks Deal

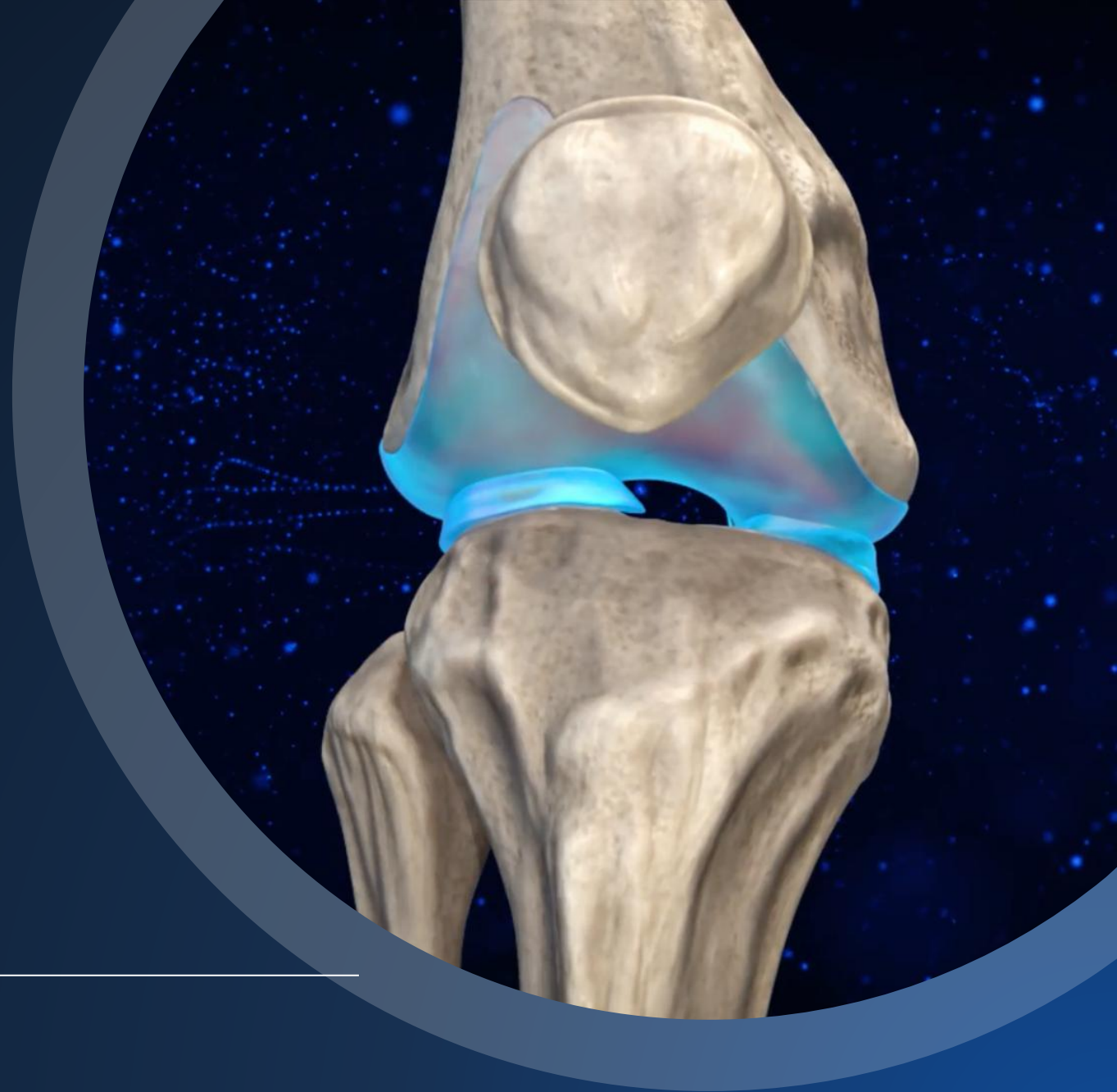
Contact: joey.bose@cytonics.com



Engineering
the **Future of**
Joint Health with
Molecular Precision

invest.cytonics.com

Join us in a *grassroots* effort to reclaim biotech
innovation from Big Pharma and Wall Street



Appendix

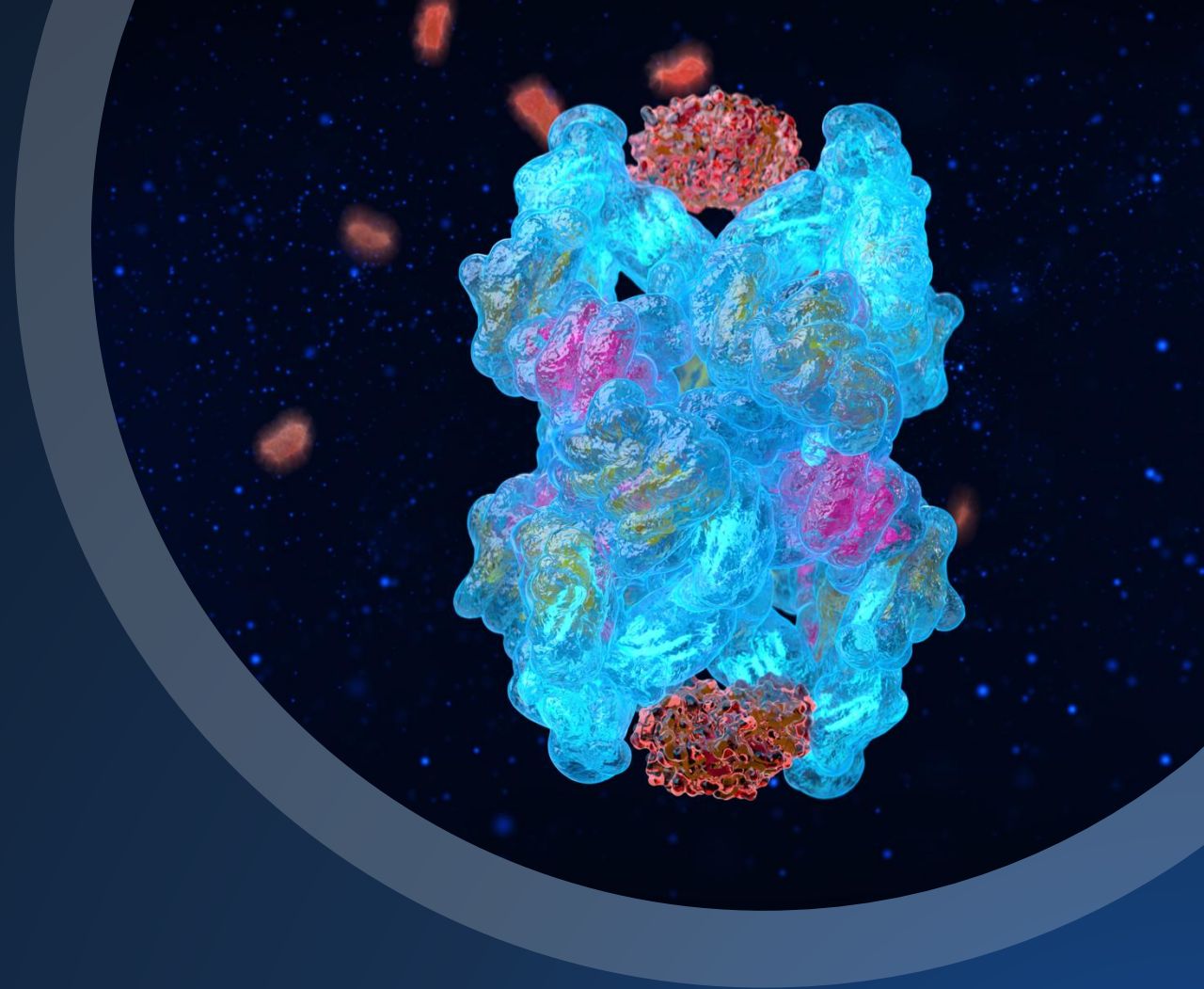
Global Patent Summary

APIC Testimonials

Scientific Publications

Supporting A2M Efficacy Data

Supplemental CYT-108 Efficacy Data



"Nature's Blueprint, Perfected."

Global Patent Summary

APIC™, FACT™, and Recombinant A2M Variant (CYT-108) Claims

COMPOSITION OF MATTER		METHODS OF USE / TREATMENT	DEVICES
AUTOLOGOUS "APIC™"	RECOMBINANT "CYT-108"		
Liquid A2M composition from blood <ul style="list-style-type: none"> ➤ GB 2501611B ➤ AU 2013222414 ➤ U.S. 10,265,388 ➤ CA 3,095,010 ➤ U.S. 18/777,657 	CYT-108 engineered bait region <ul style="list-style-type: none"> ➤ GB 2503131B ➤ U.S. 10,400,028 ➤ U.S. 10,940,189 ➤ U.S. 12,195,521 ➤ U.S. 18/947,045 ➤ U.S. 18/777,657 	Method of treating chronic wounds with autologous A2M <ul style="list-style-type: none"> ➤ U.S. Pat. No. 9,352,021 	APIC flow filtration module + centrifuge <ul style="list-style-type: none"> ➤ GB2522561B
Non-immunogenic Liquid A2M composition <ul style="list-style-type: none"> ➤ AU 2013222414 	CYT-108 bait region comprises protease recognition sites <ul style="list-style-type: none"> ➤ GB 2503131B ➤ U.S. 10,400,028 ➤ U.S. 10,940,189 	Method of treating chronic wounds with autologous A2M at 1.1x higher than sample <ul style="list-style-type: none"> ➤ U.S. Pat. No. 9,352,021 	DIAGNOSTICS Detection of FAC biomarker <ul style="list-style-type: none"> ➤ U.S. 10,889,631
A2M Enriched by +1.1x (10%+) <ul style="list-style-type: none"> ➤ GB 2501611B ➤ AU 2013222414 ➤ U.S. 10,265,388 	CYT-108 protease Inhibition <ul style="list-style-type: none"> ➤ GB 2503131B ➤ U.S. 10,889,631 ➤ EP 3221341 ➤ DE 3221341 ➤ FR 3221341 ➤ GB 3221341 	Method of treating chronic wounds with autologous A2M + non-A2M proteins <ul style="list-style-type: none"> ➤ U.S. Pat. No. 9,352,021 	METHODS OF DEVELOPMENT Engineering recombinant A2M polypeptides <ul style="list-style-type: none"> ➤ U.S. 10,889,631
		Method of treating chronic wounds with recombinant A2M <ul style="list-style-type: none"> ➤ U.S. Pat. No. 9,498,514 	
		Autologous composition of enriched A2M to treat degenerative joint diseases <ul style="list-style-type: none"> ➤ EP 13751112.7 ➤ CA 2865170 ➤ JP 6861152 ➤ U.S. 10,889,631 ➤ CA 2,967,973 ➤ CA 3,095,010 	

➤ Issued ➤ Pending

APIC™ is Patient **Tested**, Physician **Approved**



A2M has been instrumental in treating my patients with cartilage injuries that are **otherwise not amenable to cartilage restoration procedures**... I have returned the majority of my patients who received an A2M injection to participation in sports successfully **without the use of a scalpel**.

—**David E. Dominguez, MD**, President/Owner:
3D Sports Medicine and Orthopedic Center



I have been using Cytonics' APIC kits to treat various joint pains (mostly in the knee). This is part of my regenerative medicine practice. I've seen **remarkable results** such that I have suggested that **my wife and my son** undergo treatments as well as patients.

—**Laurence Rosenfield, MD**, orthopedist,
advocate of APIC treatment for patients and family



I had a **single treatment** of Cytonics' APIC therapy, APIC. **Within 2 days the swelling and stiffness was gone** and hasn't returned 6 months later. I was so impressed with these results that I have been evangelizing for APIC treatment to my doctors and friends ever since.

—**Gabe**, patient and APIC advocate



After almost eight months of therapy and various treatments, Richard Grossman, MD told me about Cytonics and the available APIC treatment. I received my first injection in April of 2018 and **within weeks the large nodule in my Achilles had shrunk** significantly. While I was feeling much better and able to **start playing basketball and tennis again**.

—**Daryle Bobb**, patient

Scientific Publications

Zhang, Yang, et al. "*Targeted Designed Variants of Alpha 2 Macroglobulin (A2MJ) Attenuate artilage Degeneration in a Rat Model of Osteoarthritis Induced by Anterior ruciate ligament ransection.*" Arthritis Research & Therapy, vol. 19, no. 1, 2017, doi:10.1186/s13075-017-1363-4.

Abrams, Geoffrey D., et al. "*Fibronectin–Aggrecan Complex as a Marker for Cartilage Degradation in Non-Arthritic Hips.*" Knee Surgery, Sports Traumatology, Arthroscopy, vol. 22, no. 4, 2014, pp. 768—773., doi:10.1007/s0167-014-2863-2.

Bedi, Asheesh, et al. "*The Effect of Matrix Metalloproteinase Inhibition on Tendon-to-Bone Healing in a Rotator Cuff Repair Model.*" Journal of Shoulder and Elbow Surgery, vol. 19, no. 3, 2010, pp. 384—391., doi:10.1016/j.jse.2009.07.010.

Browning, Shawn R, et al. "*Platelet-Rich Plasma Increases Matrix Metalloproteinases in Cultures of Human Synovial Fibroblasts.*" The Journal of Bone and Joint Surgery-American Volume, vol. 94, no. 23, 2012, doi:10.2106/jbjs.k.01501.

Cuellar, Jason M. "*Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2MJ) Concentrate Alleviates Back Pain in FAC-Positive Patients.*" Orthopedics and Rheumatology Open Access Journal, vol. 4, no. 2, Mar. 2017, doi:10.19080/oroaj.2017.04.555634.

Demirag, Burak, et al. "*The Effect of Alpha-2 Macroglobulin on the Healing of Ruptured Anterior Cruciate Ligament in Rabbits.*" Connective Tissue Research, vol. 45, no. 1, 2004, pp. 23—27., doi:10.1080/03008200490278115.

Scientific Publications

Demirag, Burak. "Enhancement of Tendon-Bone Healing of Anterior Cruciate Ligament Grafts by Blockage of Matrix Metalloproteinases." *The Journal of Bone and Joint Surgery (American)*, vol. 87, no. 11, Jan. 2005, p. 2401., doi:10.2106/jbjs.d.01952.

Gettins, Peter, and Leon W. Cunningham. "Identification of Proton Resonances from the Bait Region of Human α_2 -Macroglobulin and Effects of Proteases and Methylamine." *Biochemistry*, vol. 25, no. 18, 1986, pp. 5011—5017., doi:10.1021/bi00366a007.

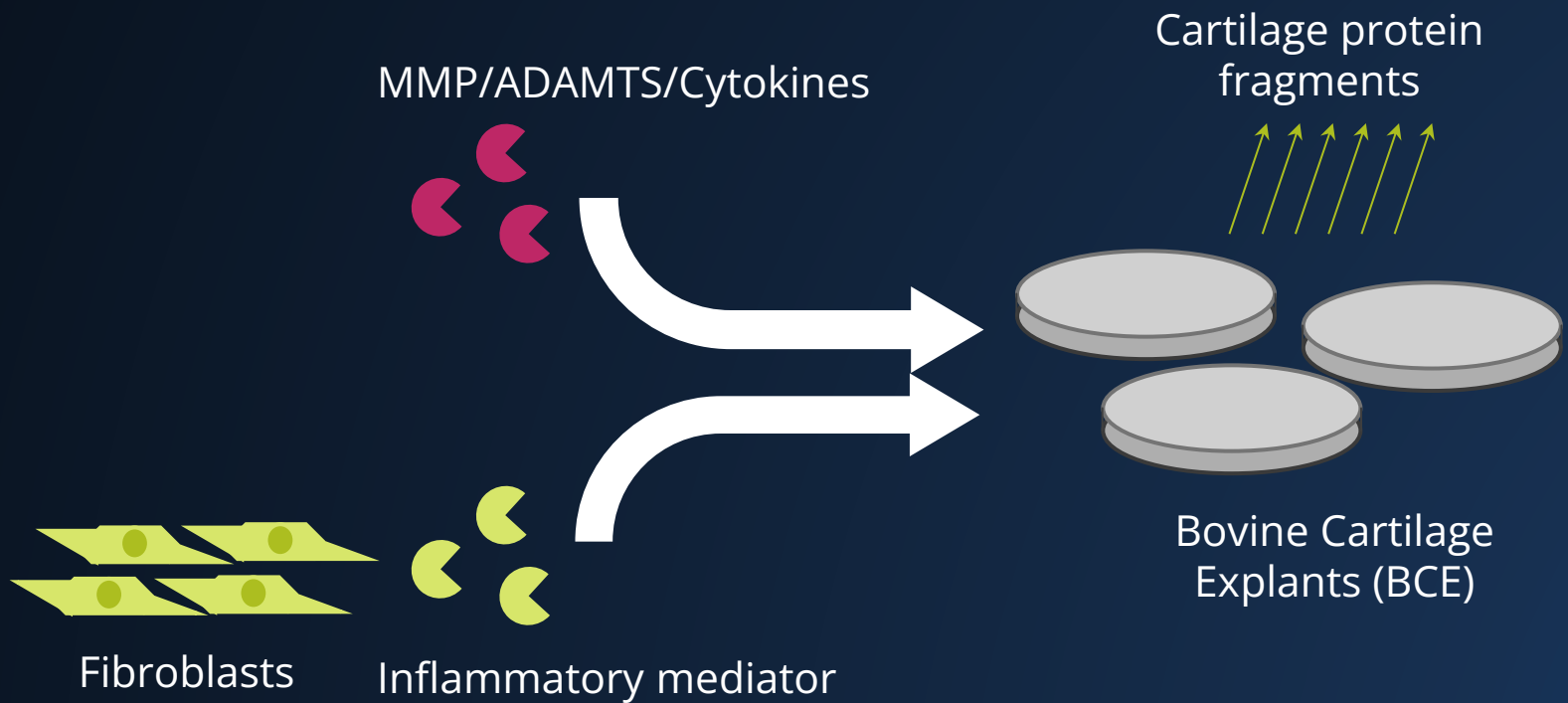
Luan, Y., et al. "Inhibition of ADAMTS-7 and ADAMTS-12 Degradation of Cartilage Oligomeric Matrix Protein by α_2 -Macroglobulin." *Osteoarthritis and Cartilage*, vol. 16, no. 11, 2008, pp. 1413—1420., doi:10.1016/j.joca.2008.03.017.

Marynen, P., et al. "A Genetic Polymorphism in a Functional Domain of Human Pregnancy Zone Protein: the Bait Region." *FEBS Letters*, vol. 262, no. 2, 1990, pp. 349—352., doi:10.1016/0014-5793(90)80226-9.

Tortorella, Micky D., et al. " α_2 -Macroglobulin Is a Novel Substrate for ADAMTS-4 and ADAMTS-5 and Represents an Endogenous Inhibitor of These Enzymes." *Journal Biological Chemistry*, vol. 279, no. 17, July 2004, of pp. 17554—17561., doi:10.1074/jbc.m313041200.

Bovine Cartilage Explants (BCE)

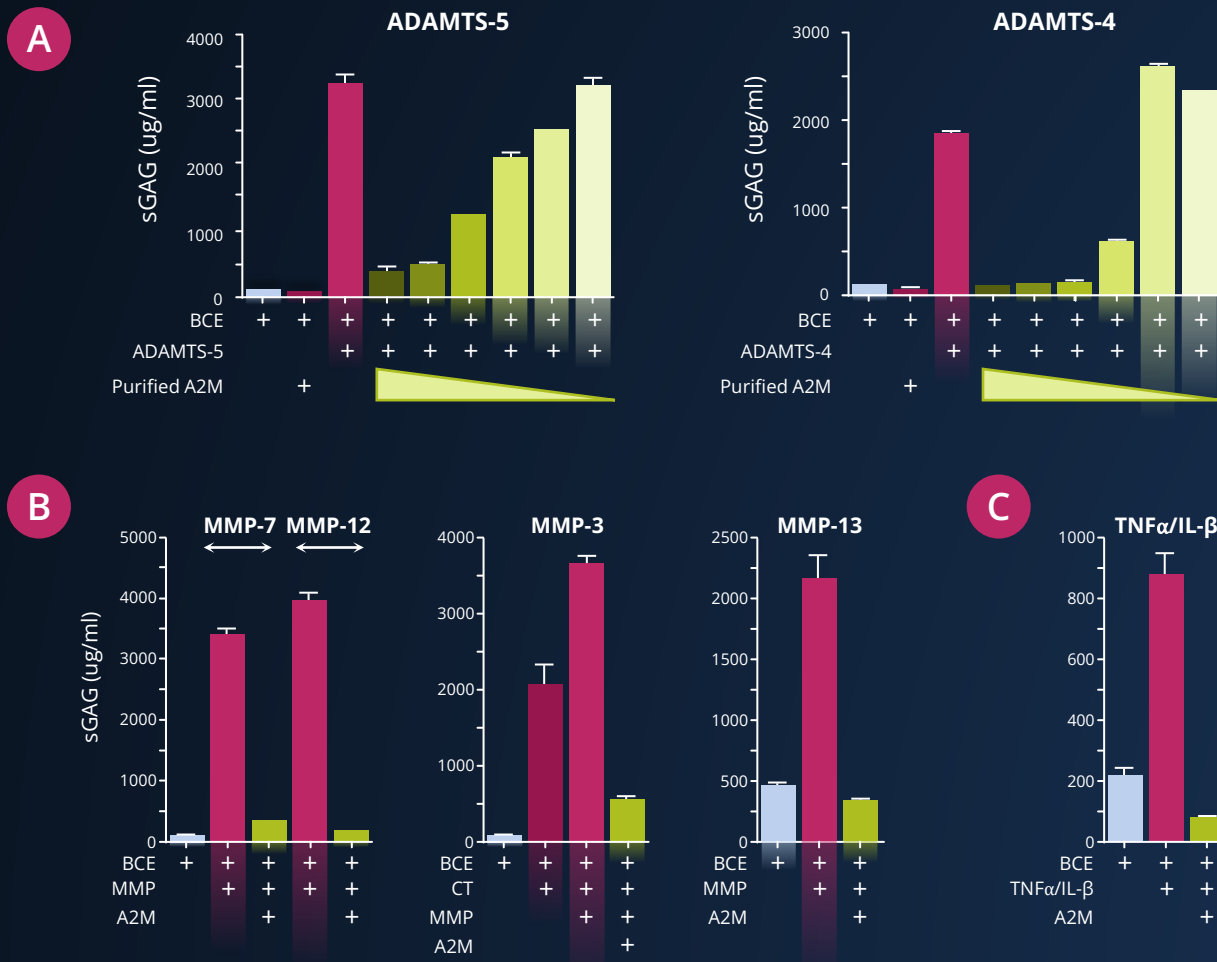
a quantitative *ex vivo* assay to measure cartilage degradation



Cartilage digestion products and protein aggregates can be detected in supernatant: *sulfated proteoglycans and glycosaminoglycans (sGAG)*

Cartilage explants can be **macroscopically graded** to assess tissue damage using *OARSI* or *Mankin scoring systems*.

Human purified A2M **reduces** protease-induced cartilage **degradation** in a dose-dependent manner



Following published BCE methods, cartilage degradation was quantified by sulfated glycosaminoglycan release (sGAG) at baseline (blue bars) and after the addition of the known catabolic enzymes, 500 ng/ml ADAMTS-4 and ADAMTS-5 (**A**), 5 ug/ml MMP-7, MMP-12, MMP-3, or MMP-13 (**B**), or the combined treatment of 80 ng/ml TNF- α and 8 ng/ml IL-1 β (**C**); all caused significant release of sGAG into the culture media (red bars). MMP-3 requires activation with chymotrypsin (CT) 30 minutes prior to treatment of BCE, which also led to digestion of cartilage and release of sGAG (purple bar). The co-administration of **purified wt-A2M (commercially available blood protein purified from plasma)** (3.1 - 100 μ g/ml) significantly reduced the augmented sGAG release by ADAMTS-5 or ADAMTS-4 in a dose-dependent manner (**A**, green bars) and addition of 100 ug/ml or 5 mg/ml purified wt-A2M was sufficient to inhibit cartilage catabolism by MMPs and proinflammatory cytokines, respectively. Values mean +/- SEM; n=5.

A2M may be the protease inhibitor responsible for the chondroprotective activity of purified blood serum

“High-IQ” Screening of A2M Variants

Relative **protease inhibitory activity** (IC50) of the recombinant A2M variants compared to wt-A2M using FITC-conjugated protease substrates.

		Cyt-98			Cyt-102			Cyt-105			Cyt-108		
		Avg	±	SD	Avg	±	SD	Avg	±	SD	Avg	±	SD
Aggrecanases	ADAMTS-4	208			290			176			201		
	ADAMTS-5 (Casein)	170	±	2	175	±	10	173	±	2	161	±	9
	ADAMTS-5 (Aggrecan)	440			194			200			246		
Collagenases	MMP-1	108	±	2	91	±	6	133	±	2	119	±	20
	MMP-8	54	±	1	81	±	3	132	±	5	64	±	2
	MMP-13	72	±	10	76	±	11	133	±	16	100	±	15
Gelatinases	MMP-2	16	±	6	65	±	6	80	±	0	37	±	6
	MMP-9	0	±	0	71	±	4	71	±	3	41	±	3
Inflam. Proteases	Elastase Cathepsin-G	117	±	7	97	±	8	147	±	5	124	±	12
		105	±	5	54	±	10	145	±	9	117	±	11

Table 3: A2M variants’ efficacy at inhibiting 9 proteases implicated in OA. Results are expressed as a percent inhibition by each variant compared to wt-A2M.

Ex vivo efficacy of A2M variants: **CYT-98** **CYT-108**

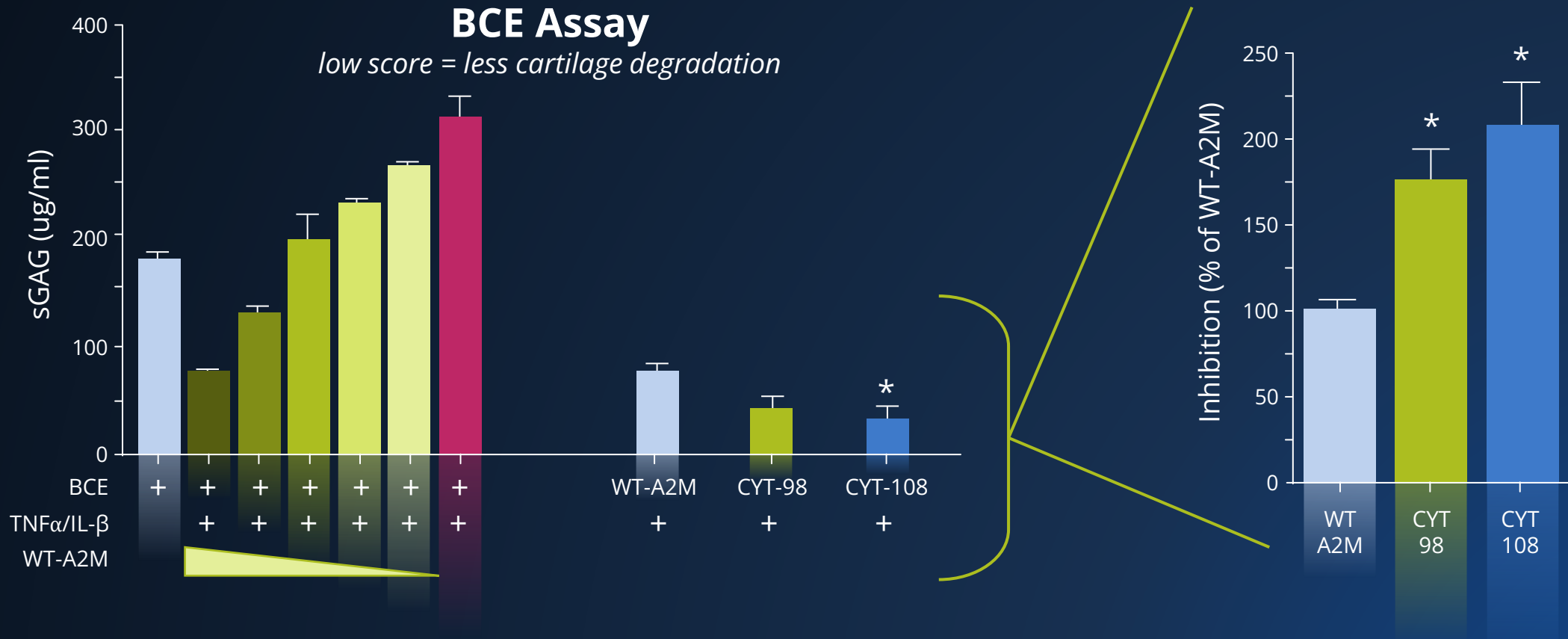
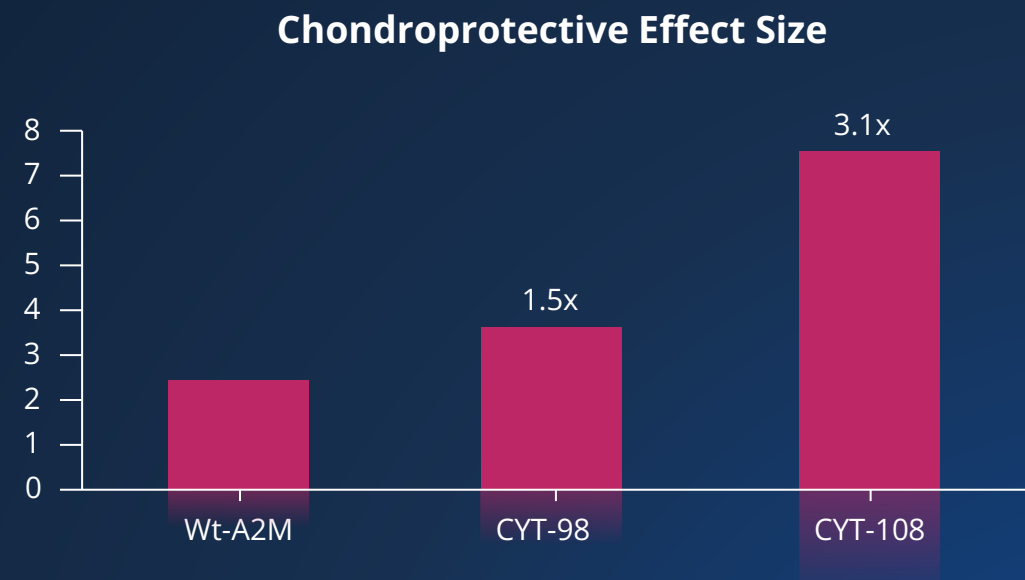
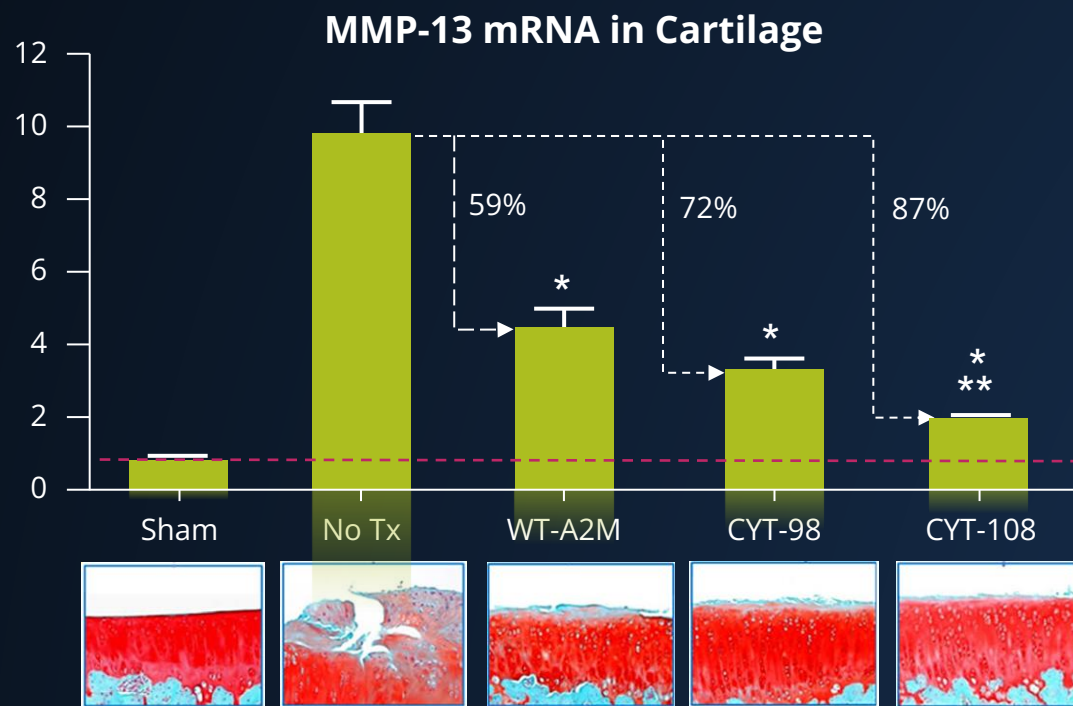


Fig. 1 Wild-type alpha-2-macroglobulin (WT-A2M) (left) and A2M variants CYT-98 and CYT-108 (right) inhibit cartilage catabolism induced by TNF α and IL-1 β . *Compared with wt-A2M, $P < 0.05$. BCE, bovine articular cartilage explants, SGAG sulfated glycosaminoglycan

Cartilage damage assessed using OARSI histological scoring

Do our A2M variants confer greater **chondroprotection** compared to wt-A2M *in vivo*?

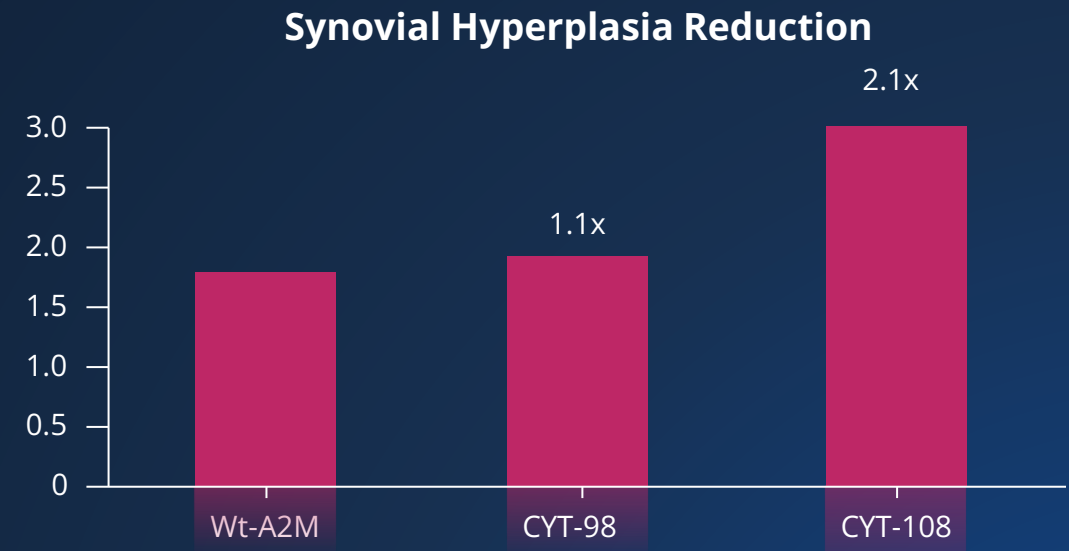
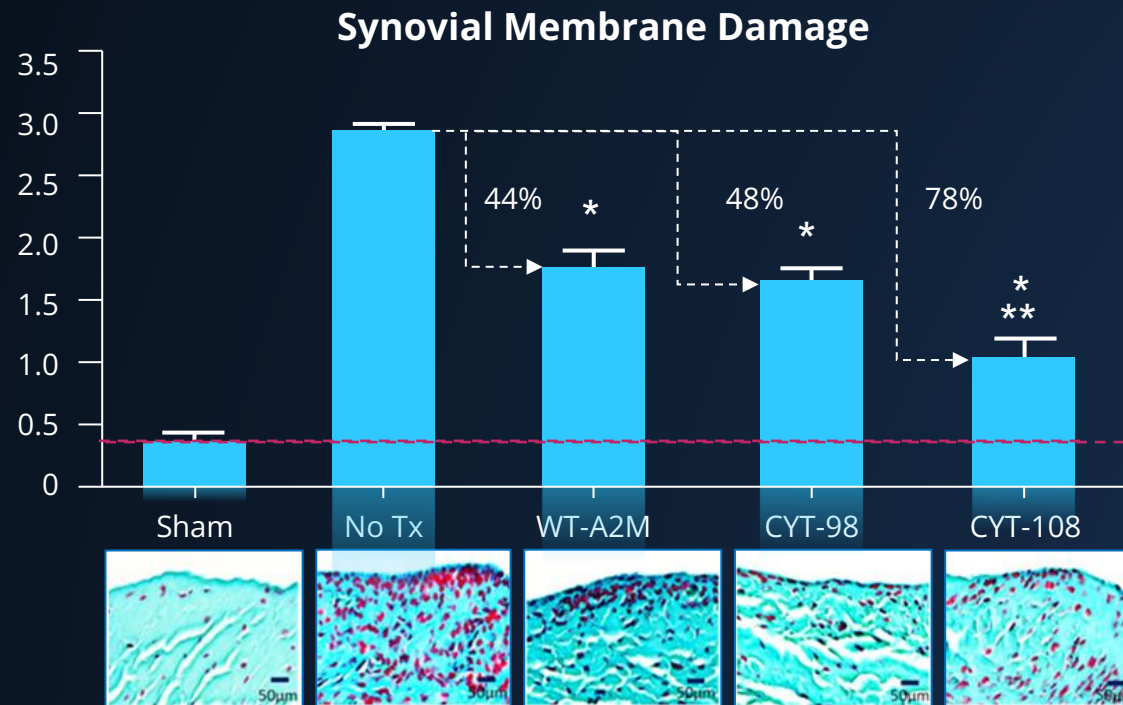


CYT-98 and CYT-108 provide 1.5-fold and 3.1-fold greater cartilage protection than wt-A2M, respectively.

Treatment with wt-A2M, CYT-98, and CYT-108 (0.153mg/ml for all) reduces cartilage damage by 59%, 72% and 87%, respectively (Sham subtracted). Values are the mean \pm SE; n=11 for each group; *compared with No Treatment (PBS), P < 0.05; ** compared with wt-A2M, P < 0.05.

Synovial membrane inflammation by histopathology

Do our A2M variants reduce **synovial hyperplasia** compared to wt-A2M in vivo?



CYT-98 and CYT-108 reduce synovial hyperplasia by 1.1-fold and 2.1-fold more than wt-A2M, respectively.

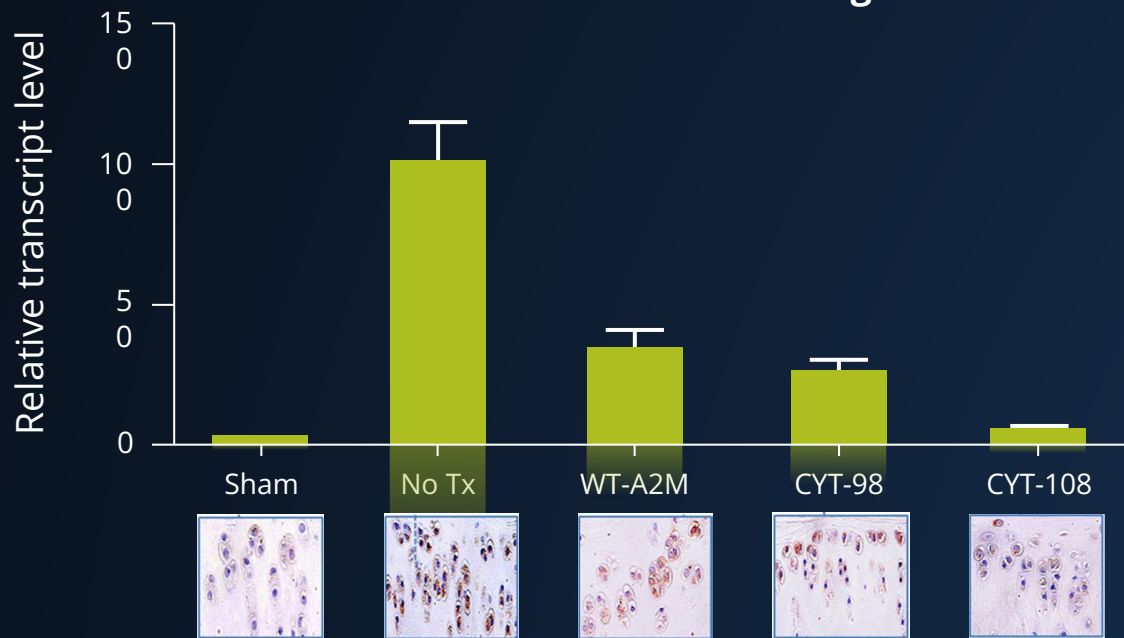
Treatment with wt-A2M, CYT-98 and CYT-108 (0.153mg/ml for all) reduced synovial hyperplasia by 44%, 48% and 78%, respectively (Sham subtracted). Values are the mean ± SE; n=11 for each group; *compared with No Treatment (PBS), P < 0.05; ** compared with wt-A2M, P < 0.05.

Zhang, Y., Wei, X., Browning, S. et al. Targeted designed variants of alpha-2-macroglobulin (A2M) attenuate cartilage degeneration in a rat model of osteoarthritis induced by anterior cruciate ligament transection. *Arthritis Res Ther* 19, 175 (2017). <https://doi.org/10.1186/s13075-017-1363-4>

MMP-13 in synovial fluid and cartilage

How do our A2M variants affect **MMP-13 expression** compared to (natural) wt-A2M?

MMP-13 mRNA in Cartilage



Rt-PCR provides further evidence that treatment with our A2M variants reduces MMP-13 transcription >3-fold compared to wt-A2M in rat cartilage tissue. The disease modifying effects of our A2M variants may not be limited to modulating protease activity and may act on transcriptional and translational pathways. Values are the mean ± SE. *Compared with No Treatment (ACLT + PBS), P < 0.05; **Compared with wt-A2M, P < 0.05;

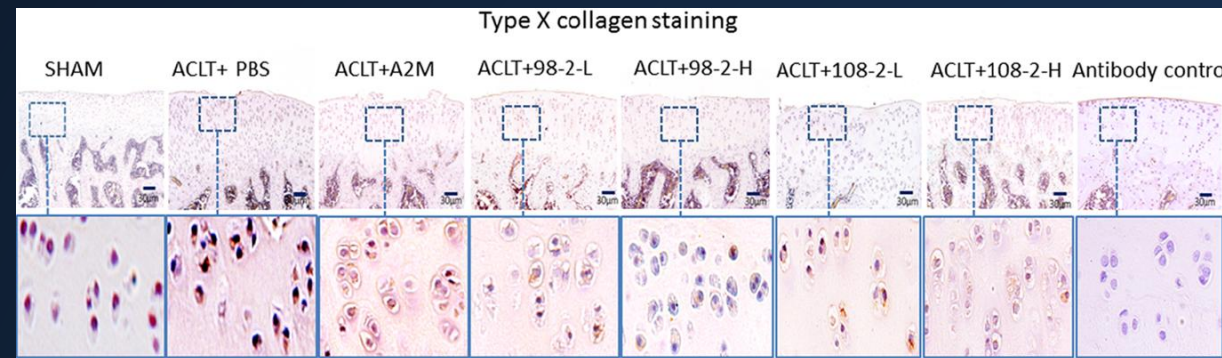
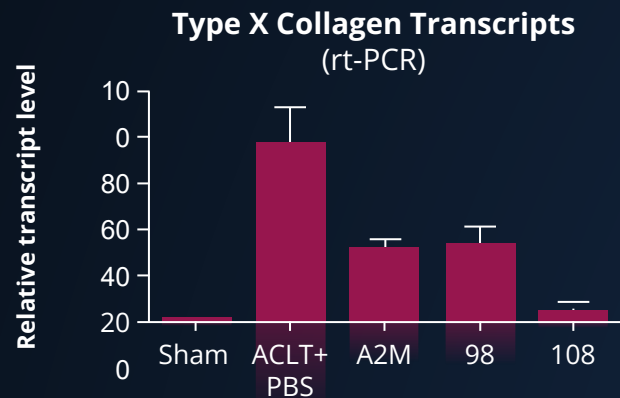
MMP-13 Levels in Synovial Fluid (ELISA)



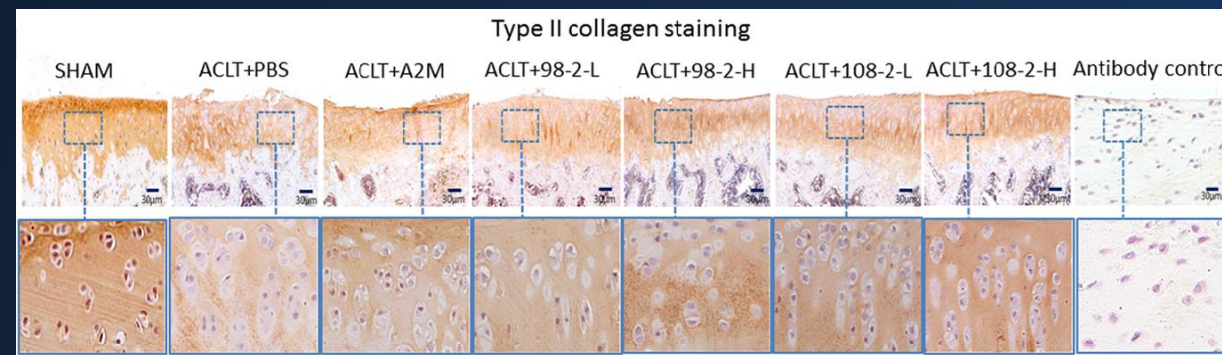
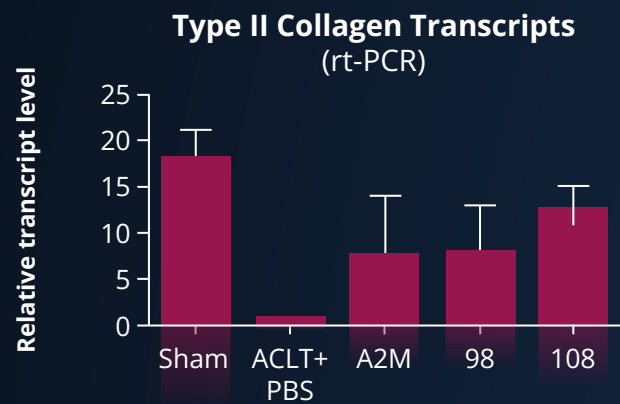
MMP-13 protein levels are significantly reduced in the synovial fluid of rats treated with wt-A2M, CYT-98, and CYT-108. Values are the mean ± SE. *Compared with No Treatment, P < 0.05; **Compared with wt-A2M, P < 0.05;

Collagen in cartilage quantified by rt-PCR and IHC

How do our A2M variants affect the **protein composition** of cartilage tissue compared to wt-A2M?



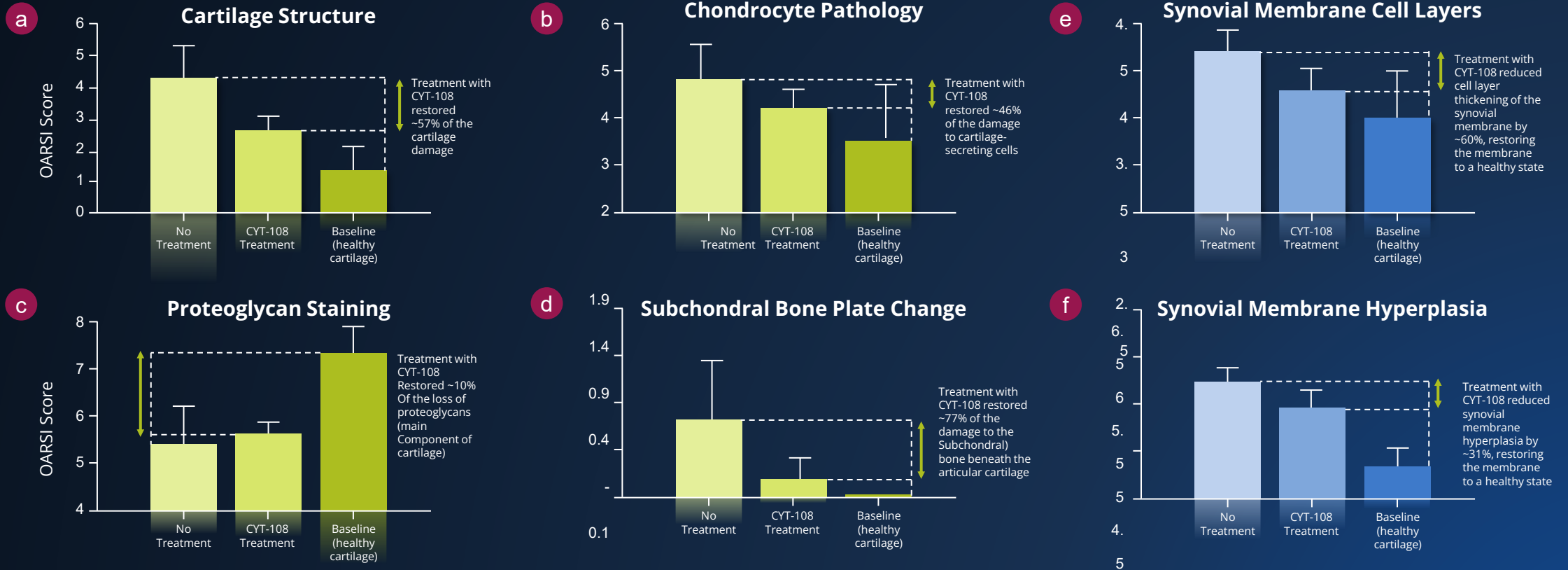
Type-X Collagen produced due to chondrocyte hypertrophy, associated with cartilage degradation and inflammation
Lighter = Good



Type II Collagen associated with normal chondrocyte physiology and healthy cartilage
Darker = Good

CYT-108 Protects Cartilage and Joint Tissue

Confirmatory preclinical efficacy experiments



Intra-articular injection of our recombinant A2M variant, CYT-108, results in articular cartilage preservation, improved remodeling of the cartilage tissue, recovery of cartilage structure and subchondral bone integrity, and preservation of synovial membrane characteristics in large animal subjects suffering from post-traumatic osteoarthritis. Histopathological grading (modified AORSI scoring system) of the articular cartilage and subchondral bone plate reveals that treatment with CYT-108 results in (a) recovery of ~57% of the damage to the cartilage structure as measured by Safranin-O staining, (b) restoration of ~46% of the damage to chondrocytes (cartilage-secreting cells), (c) enhancement of ~10% proteoglycan content (key component of cartilage), and (d) reduction of ~77% of the subchondral bone plate (bone underneath the cartilage) thickness back to normal levels. Histopathological grading (modified OARSI scoring system) of the synovial membranes of subjects in Groups 1-3 reveals that treatment with CYT-108 results in (e) reduction of ~60% of the pathological accumulation of cell layers in the synovial membrane and (f) reduction of 31% of synovial tissue hyperplasia (pathological membrane thickening) back to normal levels. Taken together, this data indicates that CYT-108 has therapeutic effect in preserving normal articular cartilage, bone, and synovial membrane physiology when administered to animals suffering from post-traumatic osteoarthritis, and substantially restores the cartilage matrix, underlying subchondral bone, and the synovial membrane back to normal, healthy anatomy and physiology. *Error bars +/- SEM.*

Forward Looking Statements

This presentation/marketing piece contains forward-looking statements. These statements may include the words "believe", "expect", "anticipate", "intend", "plan", "estimate", "project", "will", "may", "targeting" and similar expressions as well as statements other than statements of historical facts including, without limitation, those regarding the financial position, business strategy, plans, targets and objectives of the management of [](the "Company") for future operations (including development plans and objectives). Such forward-looking statements involve known and unknown risks, uncertainties and other important factors which may affect the Company's ability to implement and achieve the economic and monetary policies, budgetary plans, fiscal guidelines and other development benchmarks set out in such forward-looking statements and which may cause actual results, performance or achievements to be materially different from future results, performance or achievements expressed or implied by such forward-looking statements. Such forward-looking statements are based on numerous assumptions regarding the Company's present and future policies and plans and the environment in which the Company will operate in the future. Furthermore, certain forward-looking statements are based on assumptions or future events which may not prove to be accurate, and no reliance whatsoever should be placed on any forward-looking statements in this presentation. The forward-looking statements in this marketing piece speak only as of the date of the Company's presentation of such and the Company expressly disclaims to the fullest extent permitted by law any obligation or undertaking to disseminate any updates or revisions to any forward-looking statements contained herein to reflect any change in expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.