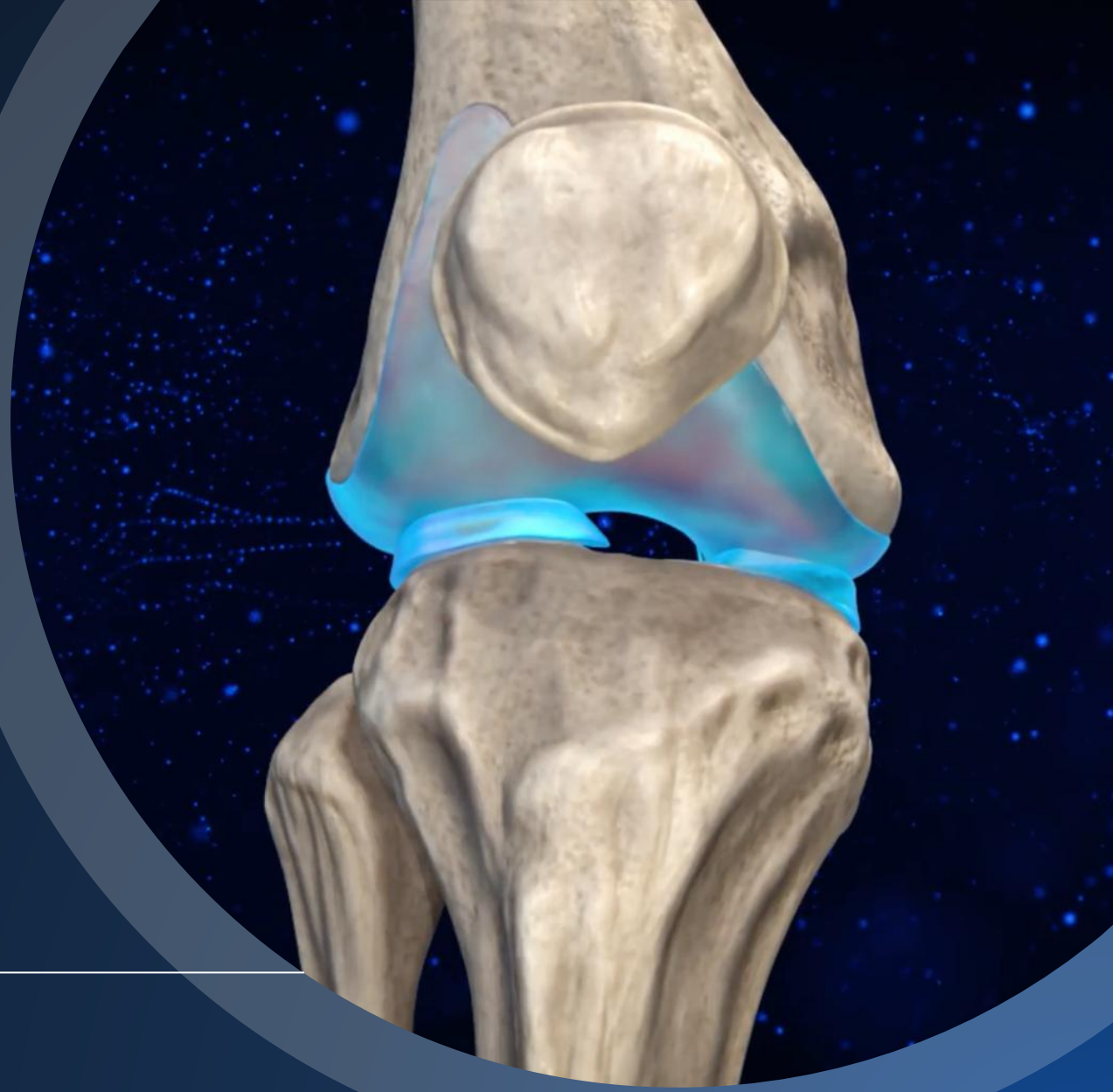
CYTONICS

# 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 A+ Disclaimer

This offering is made pursuant to Regulation A under the Securities Act of 1933. An offering statement on Form 1-A relating to the securities of Cytonics Corporation has been filed with and qualified by the Securities and Exchange Commission (SEC). The information contained in this communication is for informational purposes only and is not an offer to sell nor a solicitation of an offer to buy any securities. Any such offer or solicitation will be made only by means of an offering circular. Investing in our securities involves a high degree of risk. You should carefully consider the risk factors described in our offering circular before making an investment decision. You may obtain a copy of the offering circular by visiting the SEC's website. Forward-looking statements, including, but not limited to, projections or expectations of future performance, are inherently uncertain and involve risks and uncertainties. Actual results may differ materially from those set forth in such forward-looking statements. No assurances can be given that the issuer will attain its objectives or that the value of the securities will increase. We do not undertake any obligation to update or revise any forward-looking statements. The SEC and any state securities commission have not approved or disapproved these securities or passed upon the accuracy or adequacy of the offering circular. Any representation to the contrary is a criminal offense.

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*"He who has a Why can endure any How"*

*~ Friedrich Nietzsche*

# The What

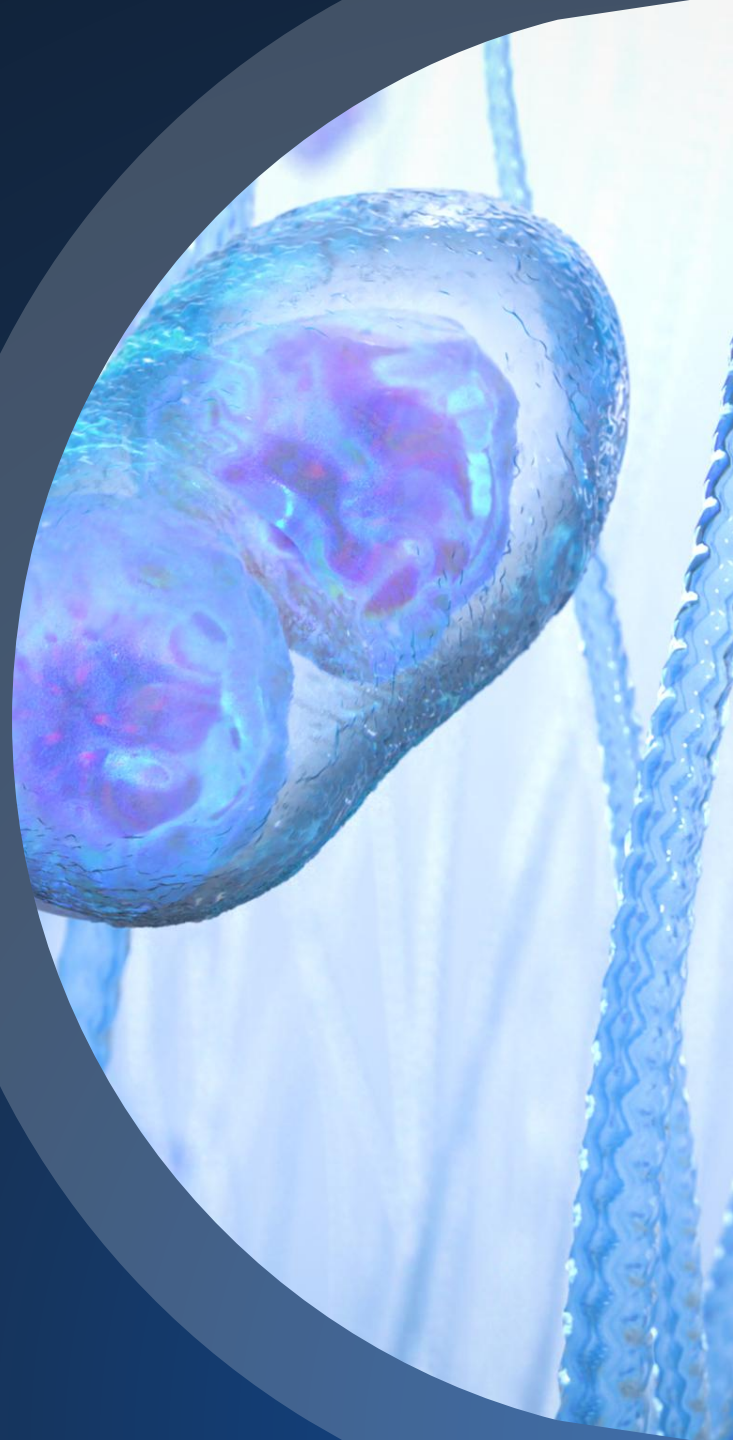
We are on a mission to develop the *first* **disease-modifying** therapy for OA, solving a problem Big Pharma has not been able to crack for decades

# The Why

Osteoarthritis is currently a life sentence of pain and debilitated quality of life due to **Big Pharma's failure**. This is simply **unacceptable**

# The How

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



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# 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

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# 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

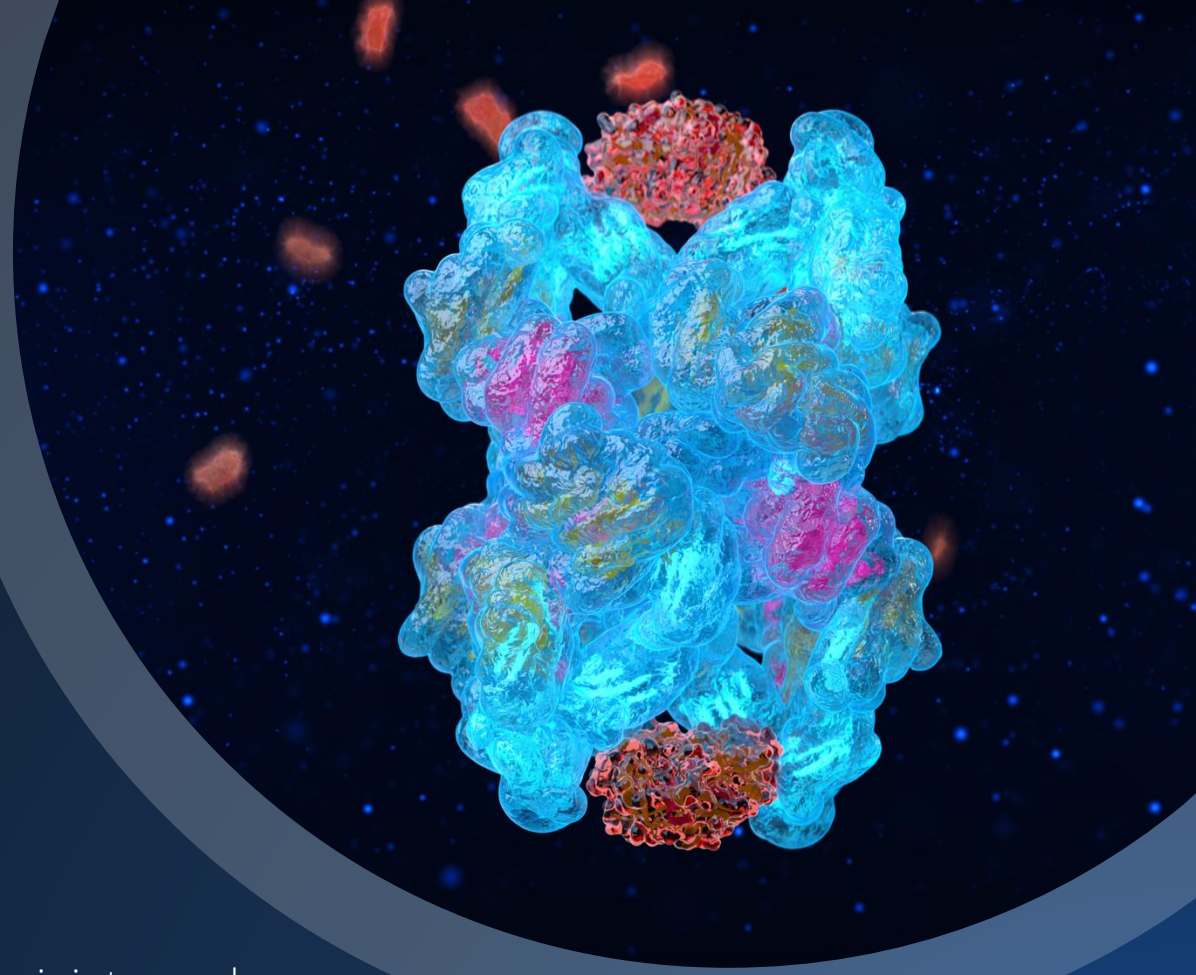
*(e.g., Prednisone)*

▼

**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

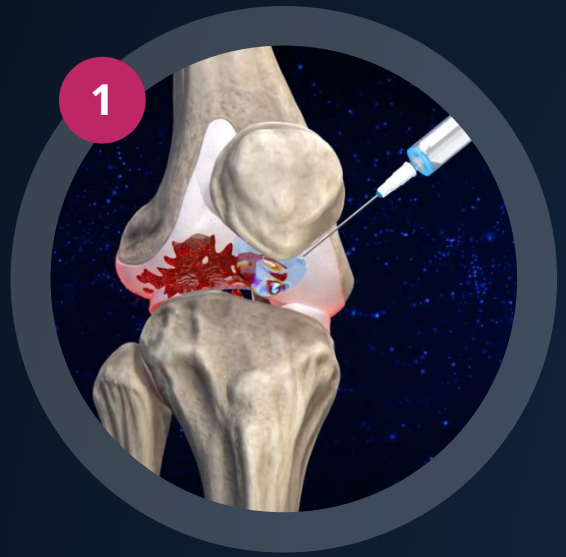
- ✓ Protease inhibitor with potent inhibitory activity against the proteases that are upregulated in OA
- ✓ Targets OA at its root cause to protect cartilage damage and the joint membrane
- ✓ Ind. research corroborates Cytonics' hypothesis that A2M can regenerate cartilage
- ✓ Highly concentrated for 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

CYTONICS®

*"Nature's Blueprint, Perfected."*

# How CYT-108 Works

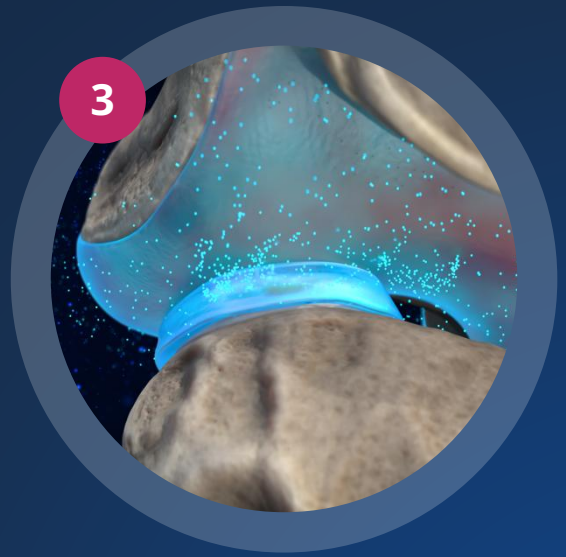
**CYT-108** is a genetically engineered **"super A2M"** protein that is **>200% more potent** than the naturally-occurring A2M protein.




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




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



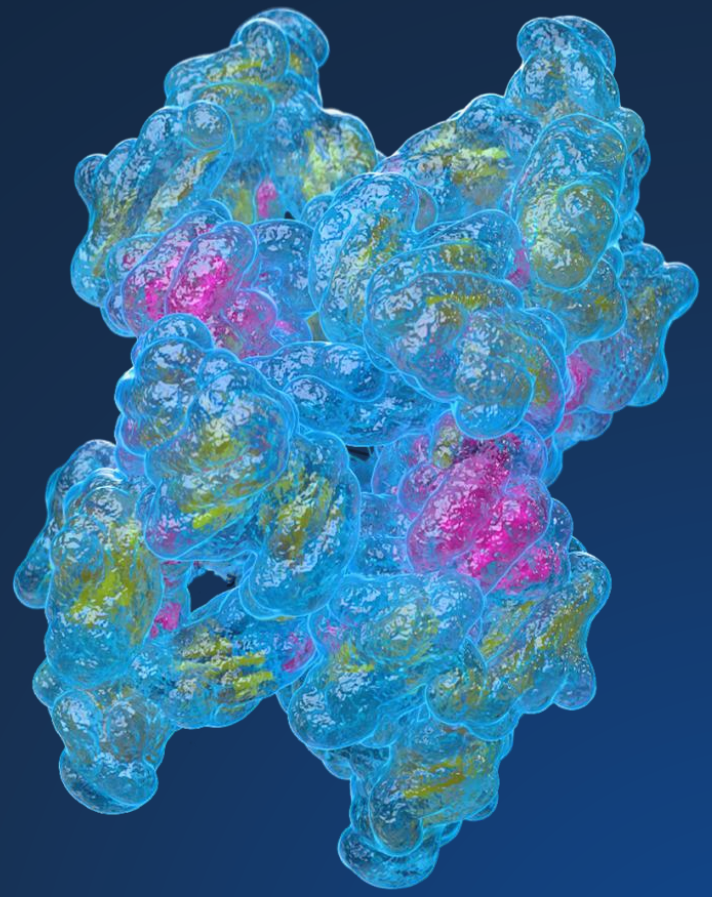

Designed to quickly reduce joint pain and inflammation while halting progressive cartilage degradation

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# 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 spac**e could bind to and inhibit the proteases, slowing and eventually **halting the progression of OA.**



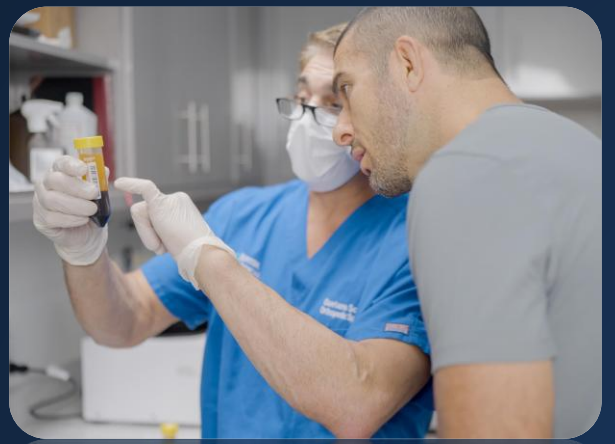
*Now, we just had to prove it.*

*See Appendix for supporting A2M efficacy data and related scientific publications*

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

## Our first-generation technology, the **A**utologous **P**rotease **I**nhibitor **C**oncentrate (**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…?*

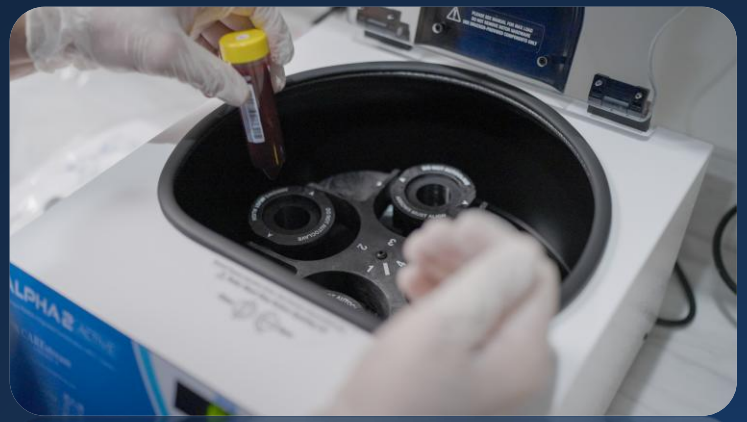
# APIC™ Blood Processing & A2M Extraction



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

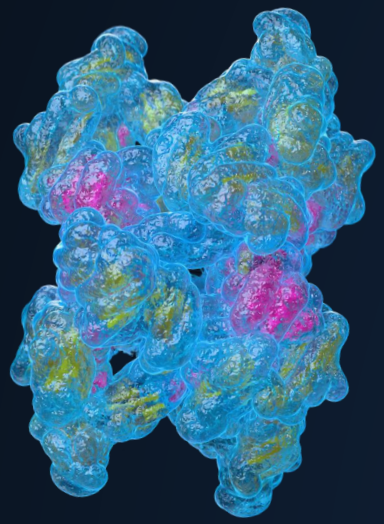


The A2M-rich concentrate is withdrawn from the APIC™ "collection" reservoir and injected directly into the patient's joint(s)

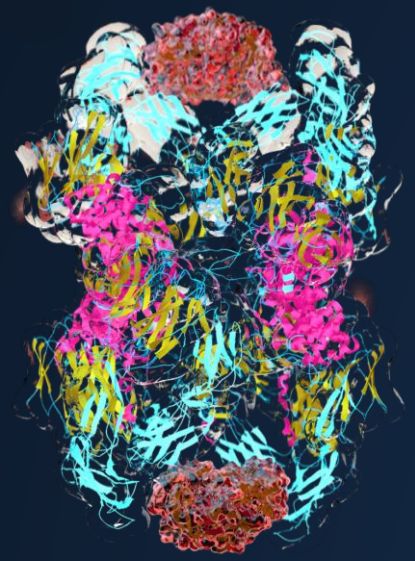
CYTONICS

# 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-3/13 and ADAMTS-4/5 |
| **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

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# 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**

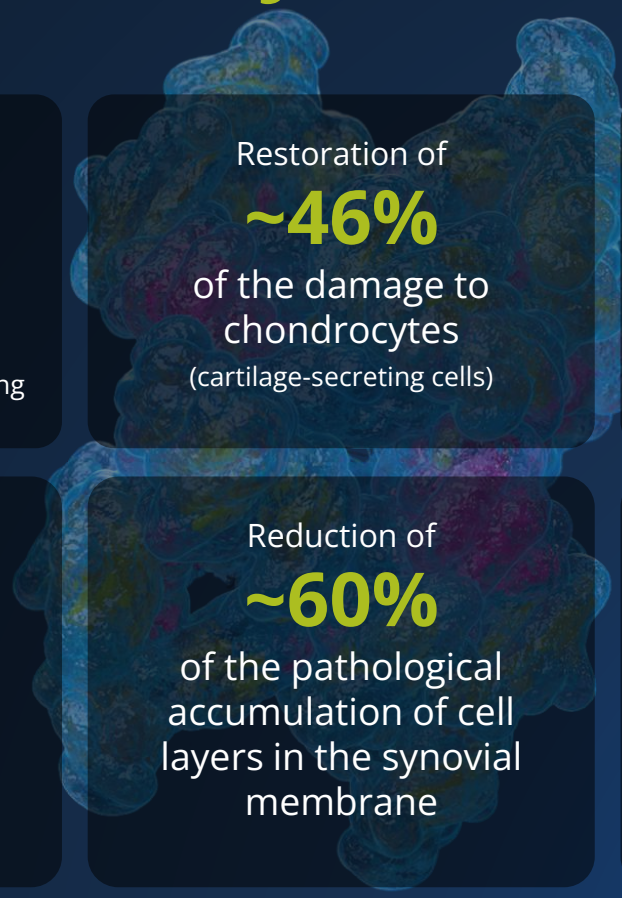


Note: The data represented in this slide is from a preclinical experiment conducted by Sinclair Research Center LLC ("Sinclair"), a Contract Research Organization located in Auxvasse, MO. Sinclair was contracted by Cytonics to perform the preclinical studies measuring the effect of CYT-108 on cartilage integrity and other joint tissues. Data was analyzed by an independent pathologist.

# 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 Safrinin-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*



Note: The data represented in this slide is from a preclinical experiment conducted by Sinclair Research Center LLC ("Sinclair"), a Contract Research Organization located in Auxvasse, MO. Sinclair was contracted by Cytonics to perform the preclinical studies measuring the effect of CYT-108 on cartilage integrity and other joint tissues. Data was analyzed by an independent pathologist.

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# 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

**Q2 2026**
Clinical Study Report

Savings up to
**$27B**
annually*

## Attractive to Insurance Payers

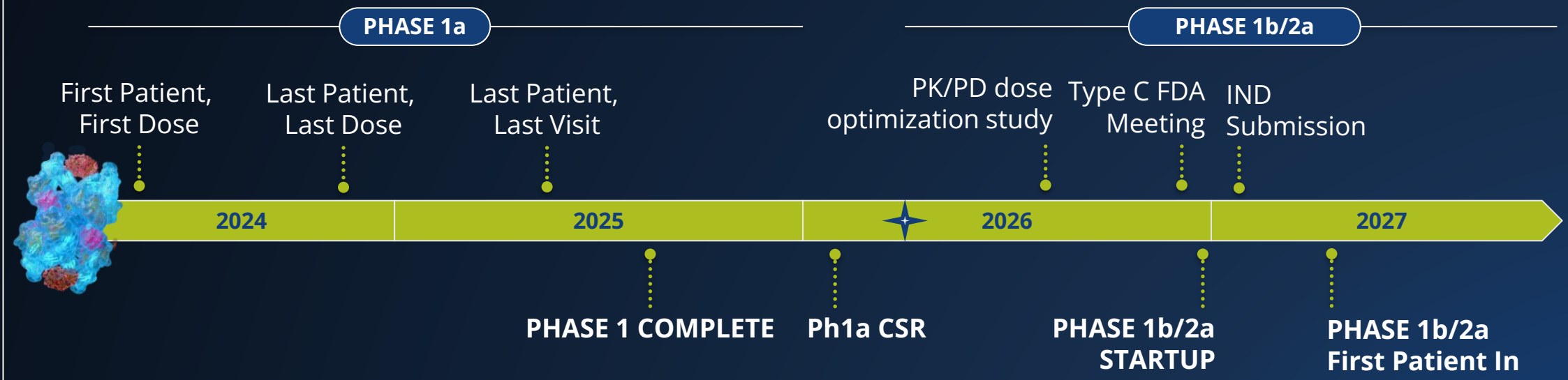
If approved, CYT-108 will be an **attractive *first-line* therapy** due to its ability to **obviate joint replacement surgeries**, as a biopharmaceutical that has demonstrable efficacy in randomized clinical trials, can be synthesized on an industrial scale and distributed globally.

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

*https://www.healthpartners.com/blog/cost-of-a-knee-replacement-surgery | 790,000 TKR surgeries conducted annually (https://anmed.org/wellness/blog/total-knee-hip-replacement-surgeries-help-millions

CYTONICS

# The Path to Success




**POTENTIAL EXIT SCENARIOS:**

**IPO**

Raise **capital** for Phase 3

Uplist to **NASDAQ**

Stock becomes **liquid** → **Shareholder ROI**

**ACQUISITION**

Acquirer buys **Phase 2b asset**

Shareholders exit via **private transaction**

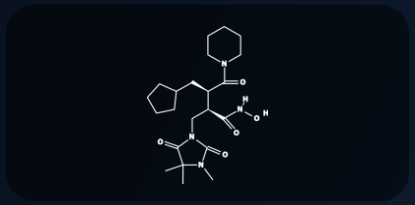
**STRATEGIC**

**Phase 2b "BioBucks":** upfront cash + milestones + royalties

IPO *or* remain private → **$$$** (dividend) + fund new **R&D** pipeline

CYTONICS

# Succeeding where Big Pharma has failed



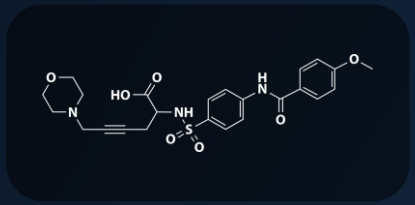
## Cipemastat (Trocade)

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



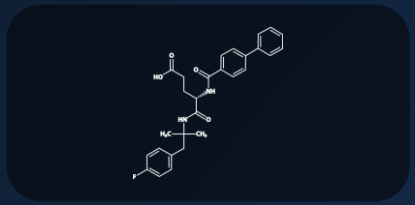
## PG-116800

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



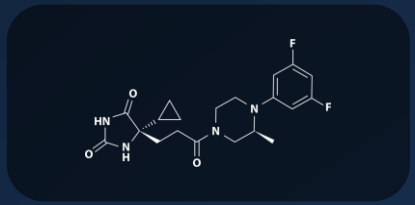
## AGG-523

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



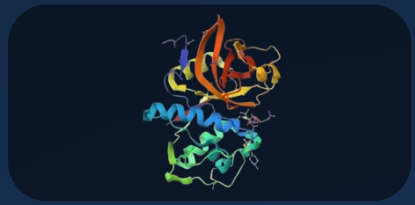
## GLPG1972 (S201086)

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

CYTONICS

# 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**

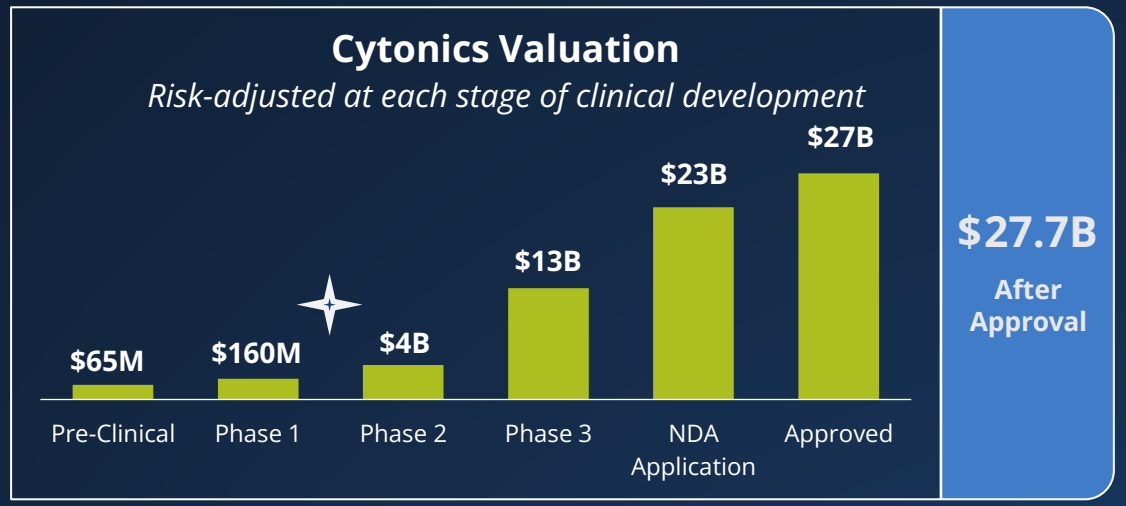
OA prevalence: https://www.who.int/news-room/fact-sheets/detail/osteoarthritis
RA prevalence: https://pubmed.ncbi.nlm.nih.gov/30285183/
RA market size: https://www.researchandmarkets.com/reports/5733874/tnf-alpha-inhibitors-global-market-report

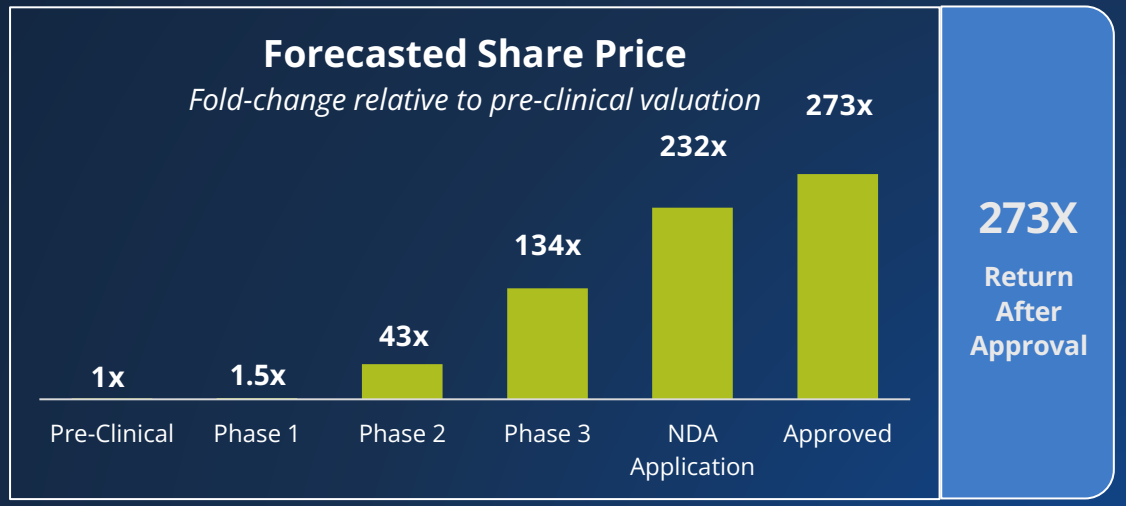
CYTONICS

# 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 company10-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 built by Cytonics using the assumptions on the left-hand side of this slide

*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.

CYTONICS

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

**Biopharma**
is almost exclusively funded 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**

Stanford University | UC San Diego

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**

University of Virginia | Johns Hopkins University

Joey Bose brings a combination of biomedical engineering, biotech investment banking, and early-stage operating experience. Educated at Johns Hopkins and the University of Virginia, he began in academic 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, leading the company from preclinical research into 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.



### Michelangelo Barone, MD

**Head of Program Operations**

Michelangelo Barone brings nearly 30 years in Big Pharma across clinical development, trial operations, and medical affairs. A trained physician, he has advanced programs from early research through approval, contributing to seven novel compounds across cardiovascular, infectious disease, vaccines, and rare diseases. He has led FDA and EMA submissions, managed inspections, and overseen global teams, gaining firsthand insight into how slow timelines, fragmented ownership, and misaligned incentives limit outcomes.

At Cytonics, he leads Program Operations, integrating clinical, CMC, and regulatory strategy into a single execution system focused on speed, efficiency, and precision. His goal is simple: streamline development, reduce friction, and execute more effectively than traditional models.

# The Team

## MANAGEMENT TEAM



### Michael Hartwich

**Head of Creative Development and Investor Relations**

Michael Hartwich leads creative development and investor relations 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 and computational methods to accelerate biological insight and therapeutic development. His work integrates data science and modeling to support discovery across complex biological systems.

With expertise in AI and bioinformatics, Alex has led teams applying predictive modeling and scalable analytics in biotech. At Cytonics, he focuses on using AI to deepen scientific understanding and support rigorous, interpretable decision-making across programs.

# 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

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# 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, Genascence Corporation



**Mukesh Ahuja, MD**

Global Clinical Head of Osteoarthritis, Paradigm Biopharmaceutical

## OUR COLLABORATORS

BROWN

The Scripps Research Institute

Stanford Medicine

Jefferson University and Hospitals

Beaumont Health System

bme University of Michigan Biomedical Engineering

FAU Florida Atlantic University

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# Self-Evident Success

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

**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 purified by 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*

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# 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**

$40M Reg A+ Equity Crowdfund

**USE OF FUNDS**

CYT-108 Phase 2 Clinical Trials

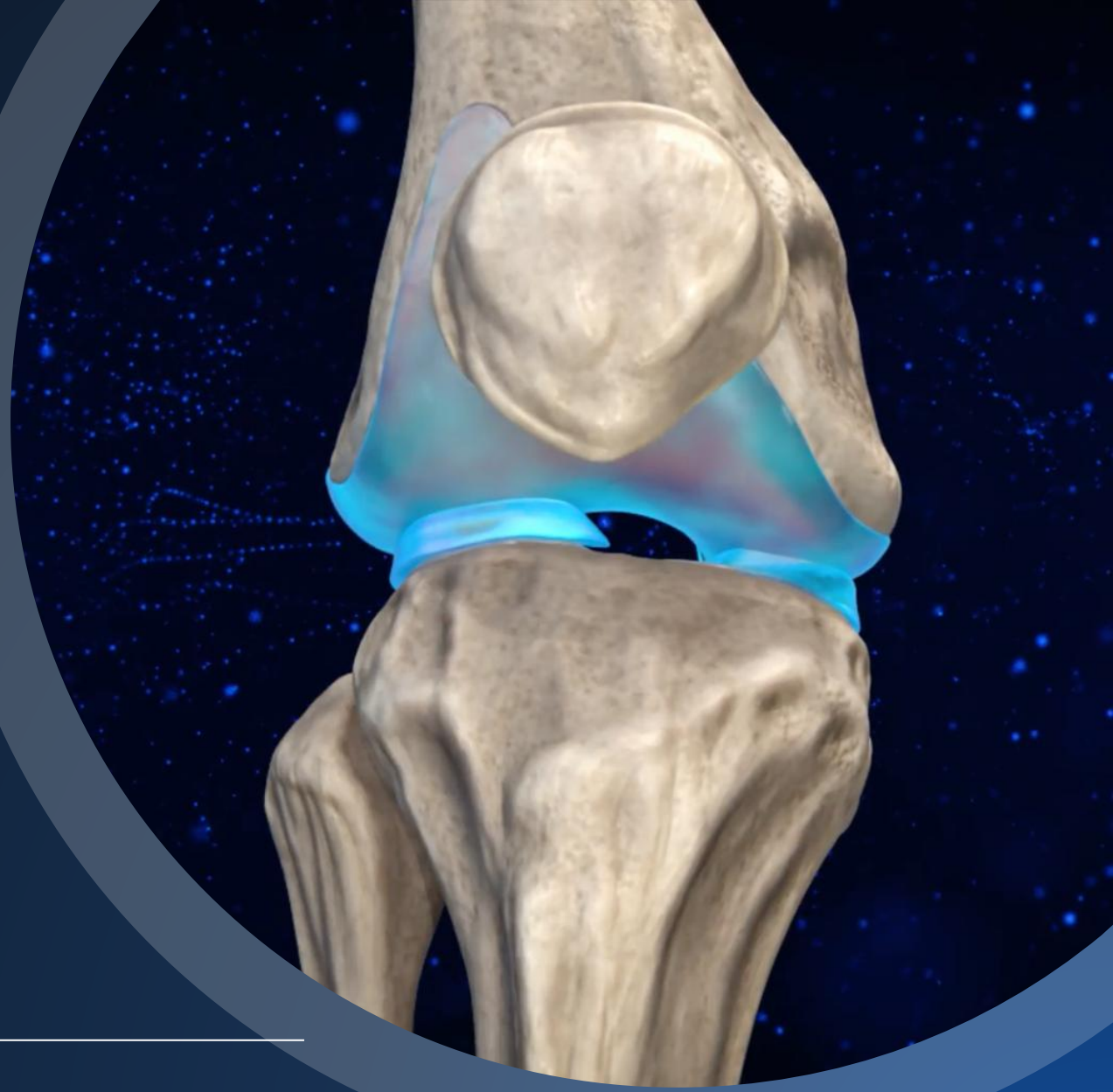
**EXIT STRATEGY**

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

Contact: Joey.bose@cytonics.com

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# Engineering the Future of Joint Health with Molecular Precision



**invest.cytonics.com**

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

# Appendix

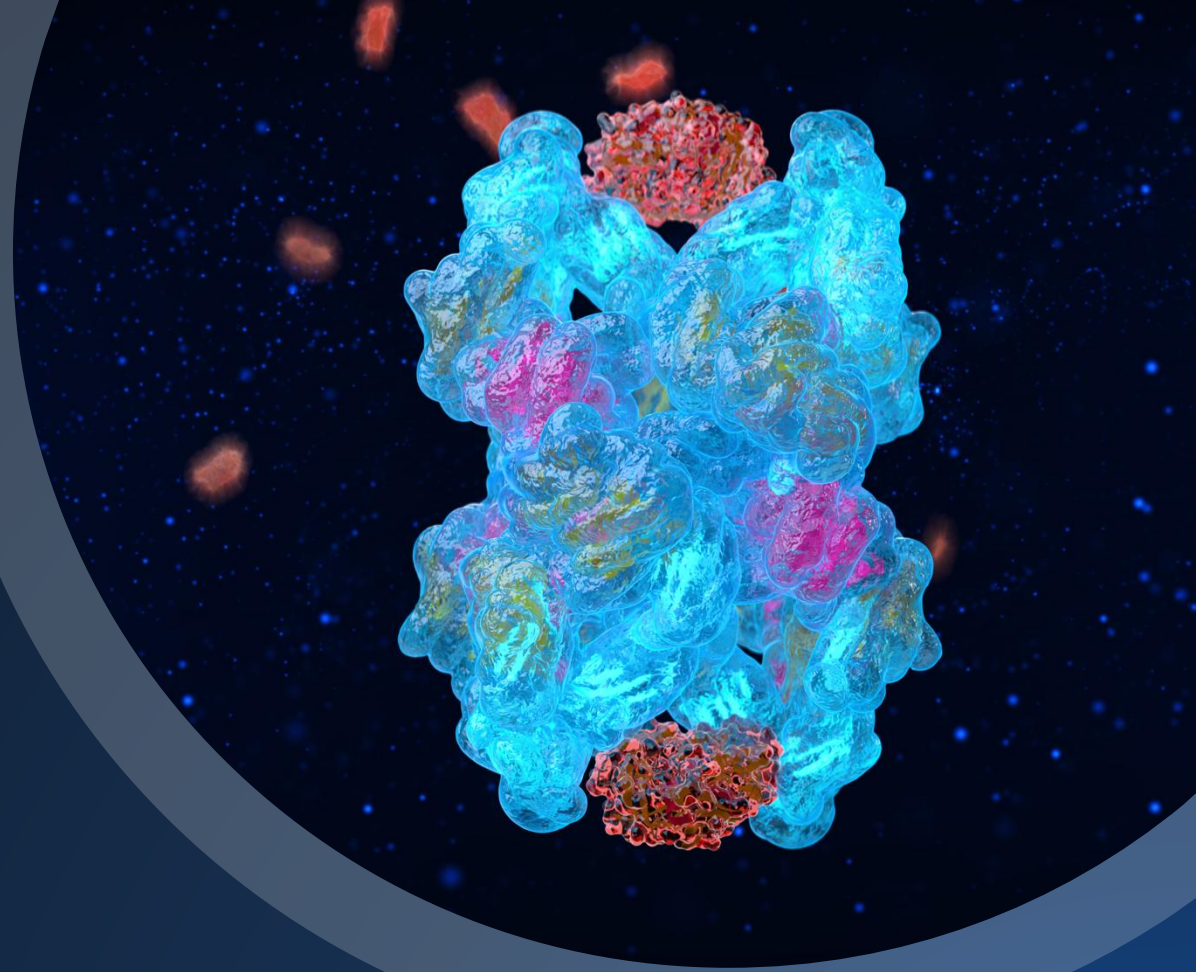
**Patent Status Summary**

**APIC Testimonials**

**Scientific Publications**

**Supporting A2M Efficacy Data**

**Supplemental CYT-108 Efficacy Data**



CYTONICS®

*"Nature's Blueprint, Perfected."*

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# Patent Status Summary

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

### COMPOSITION OF MATTER

#### AUTOLOGOUS "APIC™"

**Liquid A2M composition from blood**

- GB 2501611B
- AU 2013222414
- U.S. 10,265,388
- CA 3,095,010
- U.S. 18/777,657
- CA 2865170
- U.S.11,040,092
- EP 2827882
- GB 2827882
- FR 2827882
- DE 2827882

**Non-immunogenic Liquid A2M composition**

- AU 2013222414

**A2M Enriched by +1.1x (10%+)**

- GB 2501611B
- AU 2013222414
- U.S. 10,265,388

#### RECOMBINANT "CYT-108"

**CYT-108 engineered bait region**

- 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
- AU 2015349782
- JP 6861152
- U.S. 12,967,973

**CYT-108 bait region comprises protease recognition sites**

- GB 2503131B
- U.S. 10,400,028
- U.S. 10,940,189
- AU 2015349782
- CA 2,967,973
- U.S. 11,634,475

**CYT-108 protease Inhibition**

- GB2 503131B
- U.S. 10,889,631
- EP 3221341
- DE 3221341
- FR 3221341
- GB 3221341

### METHODS OF USE / TREATMENT

**Method of treating chronic wounds with autologous A2M**

- U.S. Pat. No. 9,352,021

**Method of treating chronic wounds with autologous A2M at 1.1x higher tha sample**

- U.S. Pat. No. 9,352,021

**Method of treating chronic wounds with autologous A2M + non-A2M proteins**

- U.S. Pat. No. 9,352,021

**Method of treating chronic wounds with recombinant A2M**

- U.S. Pat. No. 9,498,514

**Autologous composition of enriched A2M to treat degenerative joint diseases**

- EP 13751112.7
- CA 2865170
- JP 6861152
- U.S. 10,889,631
- CA 2,967,973
- CA 3,095,010

### DEVICES

**APIC flow filtration module + centrifuge**

- GB2522561B

### DIAGNOTICS

**Detection of FAC biomarker**

- U.S. 10,889,631

### METHODS OF DEVELOPMENT

**Engineering recombinant A2M polypeptides**

- U.S. 10,889,631

Issued  Pending

CYTONICS

# 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



These testimonials may not be representative of the experience of other customers and are not a guarantee of future performance or success.

# 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.

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# 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 .Alpha.2-Macroglobulin and Effects of Proteases and Methylamine."* Biochemistry, vol. 25, no. 18, 1986, pp. 5011—5017., doi:10.1021/bi00366a007.

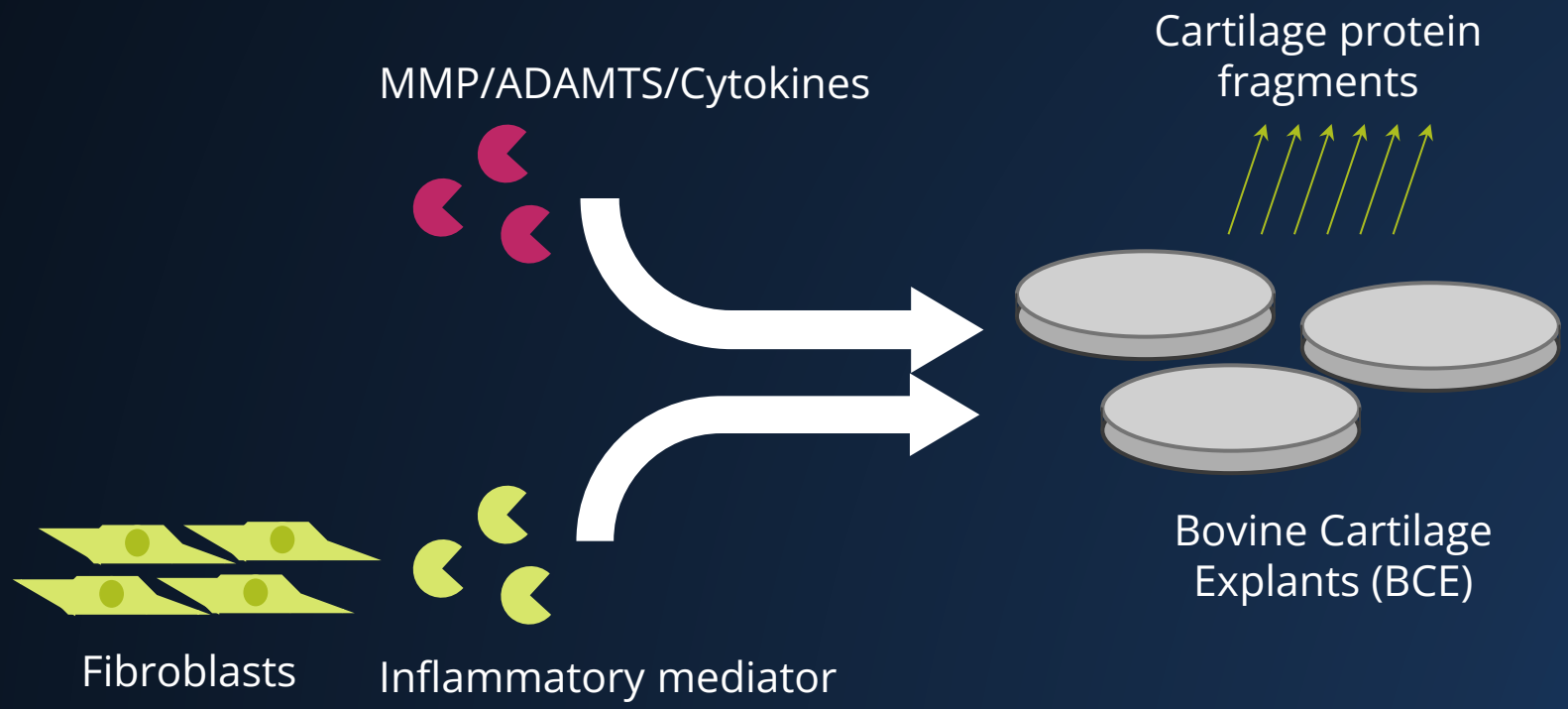
Luan, Y., et al. *"Inhibition of ADAMTS-7 and ADAMTS-12 Degradation of Cartilage Oligomeric Matrix Protein by Alpha-2-Macroglobulin."* Osteoarthritis and Cartilage, vol. 16, no. 11, 2008, pp. 1413—1420., doi:10.1016/j.joca.2008.03.017.

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. *"a2-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.

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# Bovine Cartilage Explants (BCE)
## a quantitative *ex vivo* assay to measure cartilage degradation

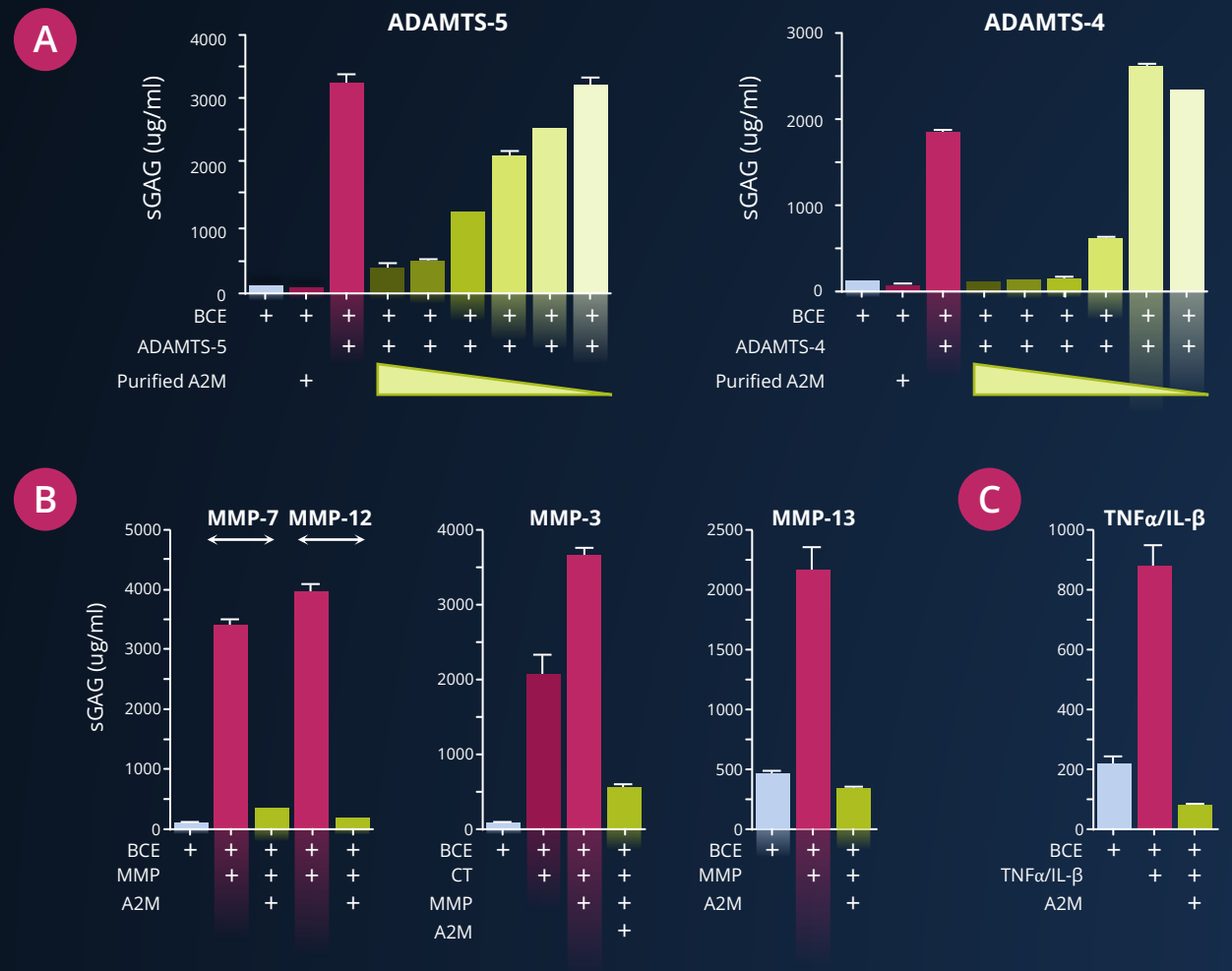



Cartilage digestion products and protein aggregates can be detected in supernatant: *sulfated proteoglycans and glycosaminoglycans (**sGAG**)*

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

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# 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-1β (**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 - 100µg/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**

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# "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 Avg ± SD | Cyt-102 Avg ± SD | Cyt-105 Avg ± SD | Cyt-108 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.

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

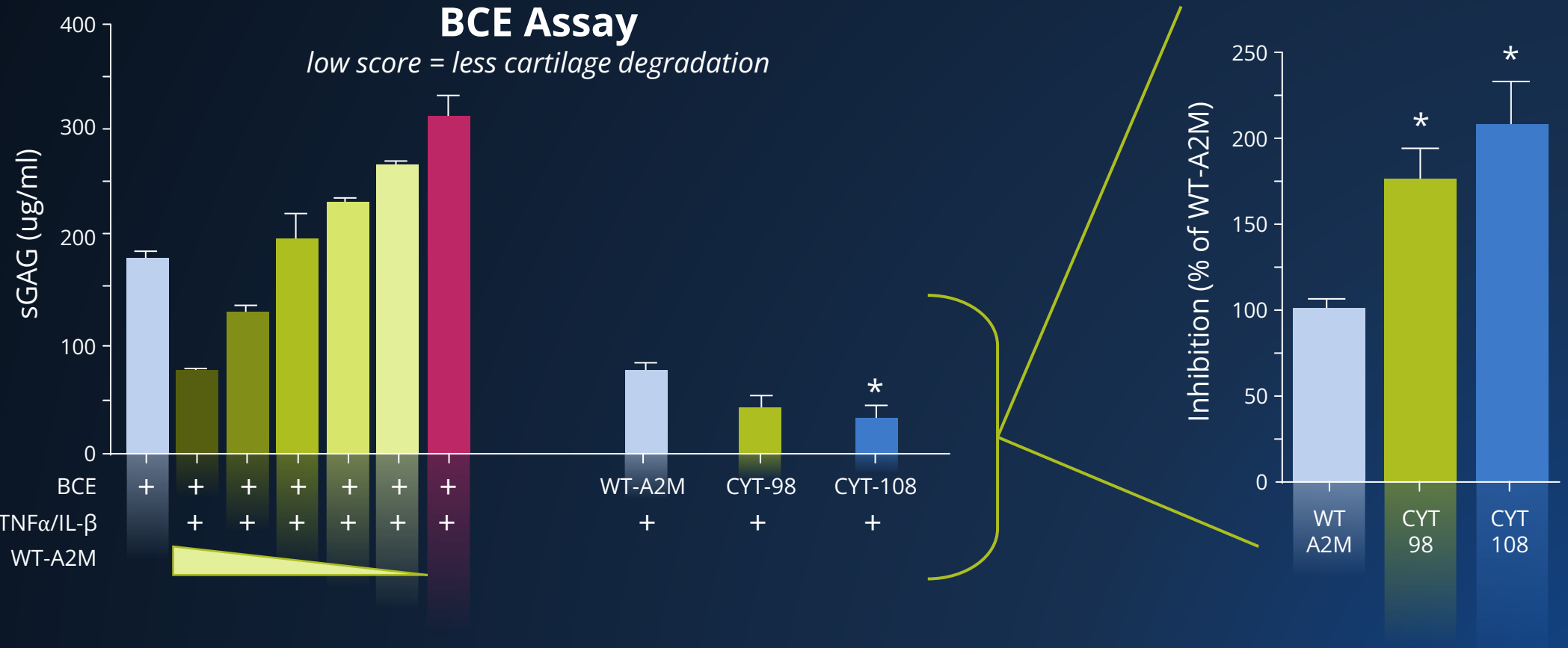



**Fig. 1** Wild-type alpha-2-macroglobulin *(WT-A2M) (left)* and A2M variants CYT-98 and CYT-108 *(right)* inhibit cartilage catabolism induced by TNFα and IL-1β. *Compared with wt-A2M, $P<0.05$. BCE, bovine articular cartilage explants, SGAG sulfated glycosaminoglycan

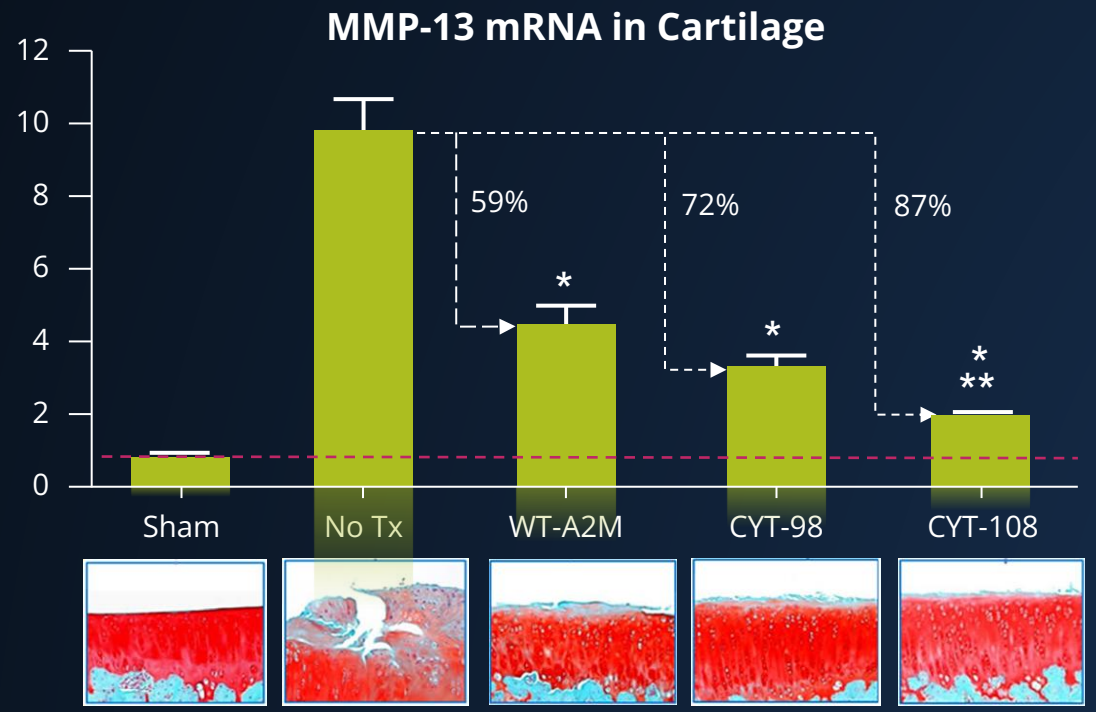


Zhang, Y., Wei, X., Browning, S. et al. Targeted designed variants of alpha-2-macroglobulin (A2M) attenuate cartilage degeneration in a rat model of osteoarthritis induced by anterior cruciate ligament transection. Arthritis Res Ther 19, 175 (2017). https://doi.org/10.1186/s13075-017-1363-4

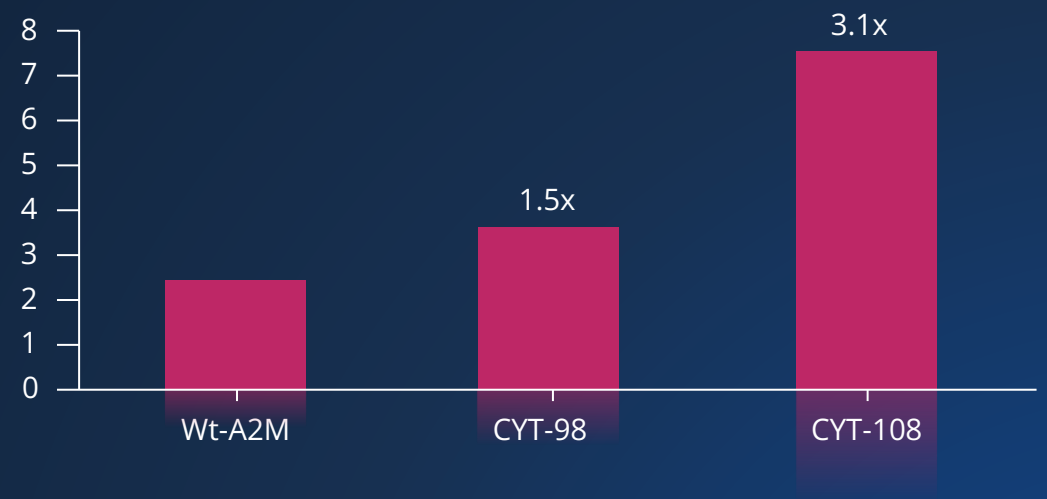
CYTONICS

# **Cartilage damage** assessed using OARSI histological scoring

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




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 ± SE; n=11 for each group; *****compared with No Treatment (PBS), $P < 0.05$; ****** compared with wt-A2M, $P < 0.05$.




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

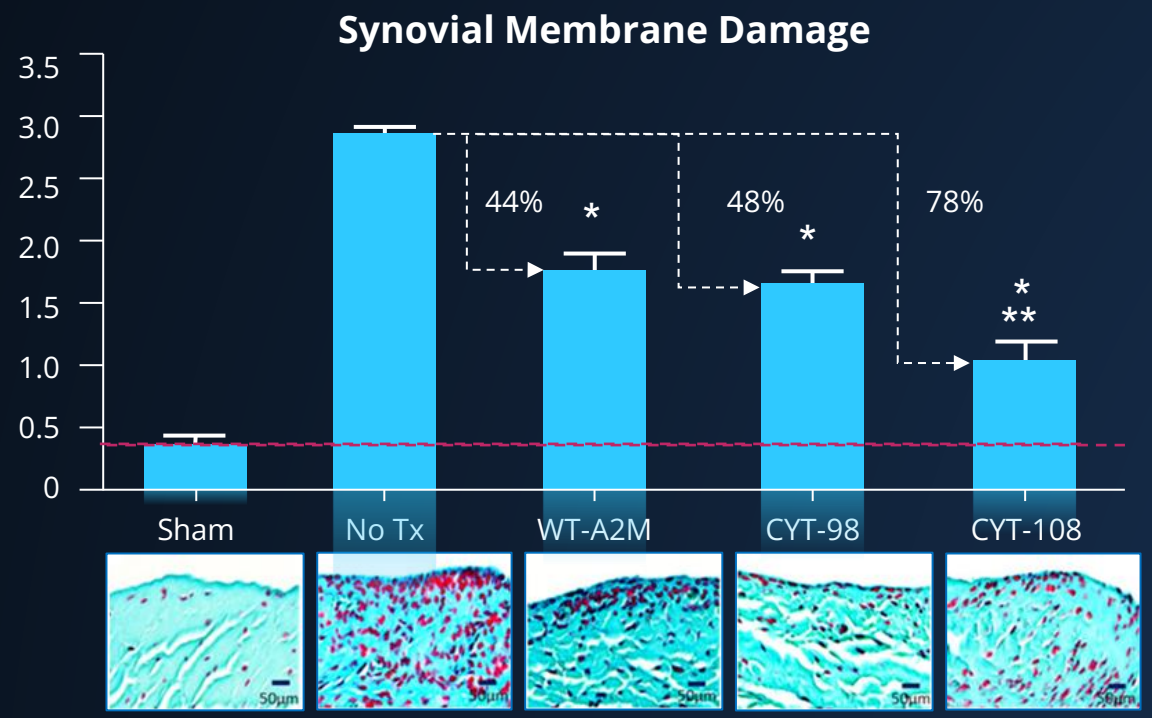


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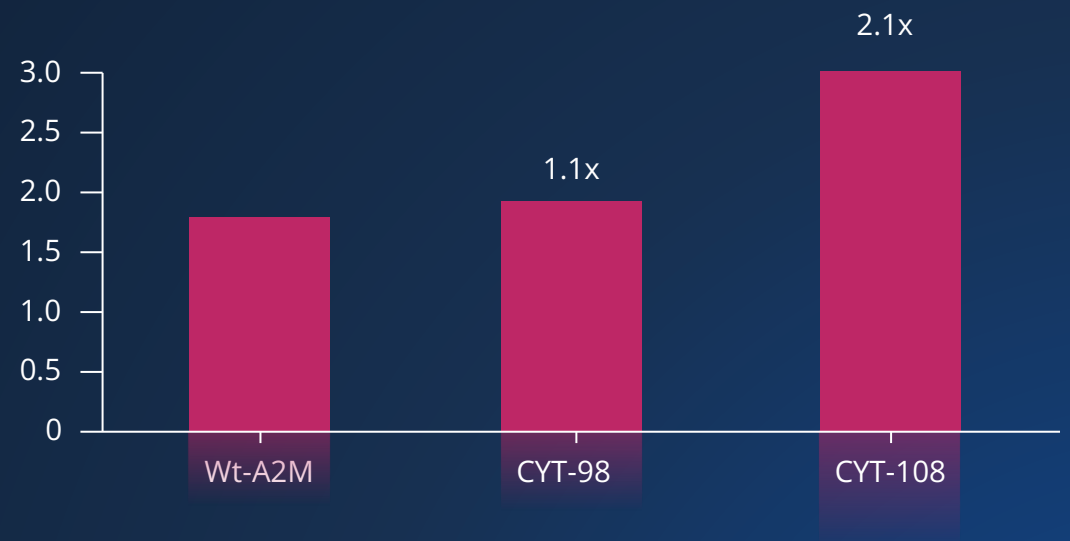
CYTONICS

# **Synovial membrane** inflammation by histopathology

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




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.




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



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

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# **MMP-13** in synovial fluid and cartilage

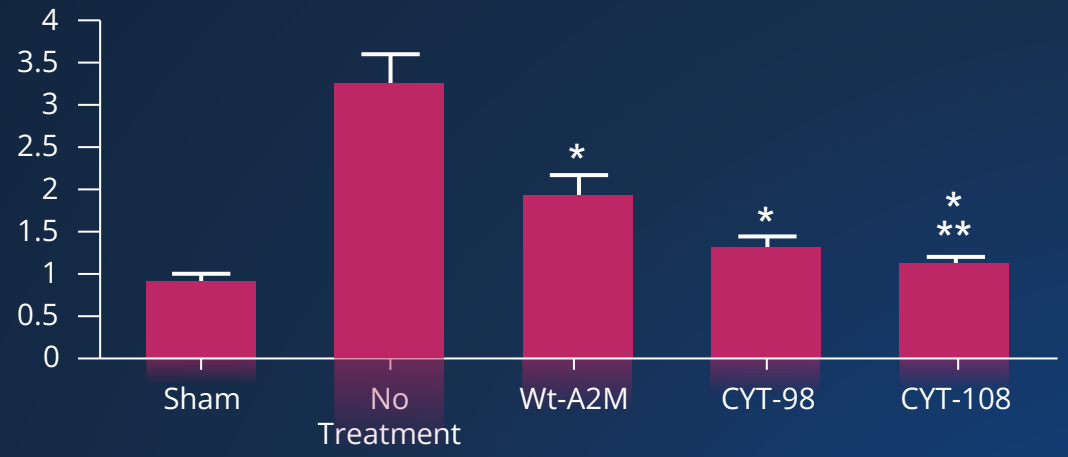
How do our A2M variants affect **MMP-13 expression** compared to (natural) wt-A2M?

**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 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)**



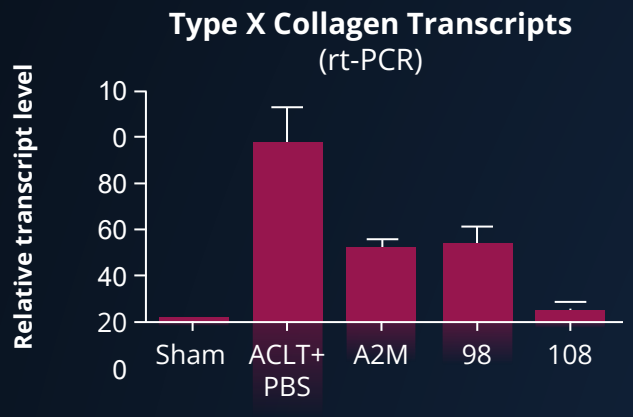

MMP-13 protein levels are significantly reduced in the synovial fluid of rats treated with wt-A2M, CYT-98, and CYT-108. Values are the mean ± SE. *Compared with No Treatment, P < 0.05; **Compared with wt-A2M, P < 0.05;

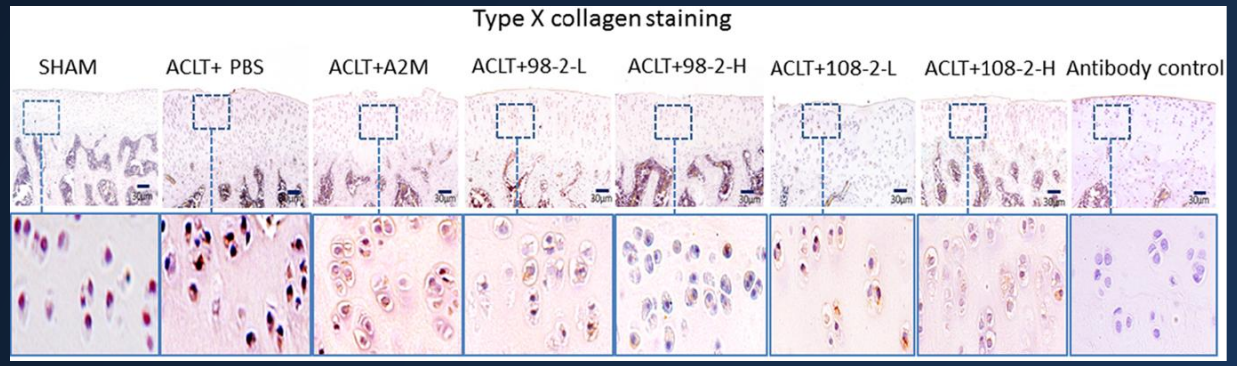


Zhang, Y., Wei, X., Browning, S. et al. Targeted designed variants of alpha-2-macroglobulin (A2M) attenuate cartilage degeneration in a rat model of osteoarthritis induced by anterior cruciate ligament transection. Arthritis Res Ther 19, 175 (2017). https://doi.org/10.1186/s13075-017-1363-4

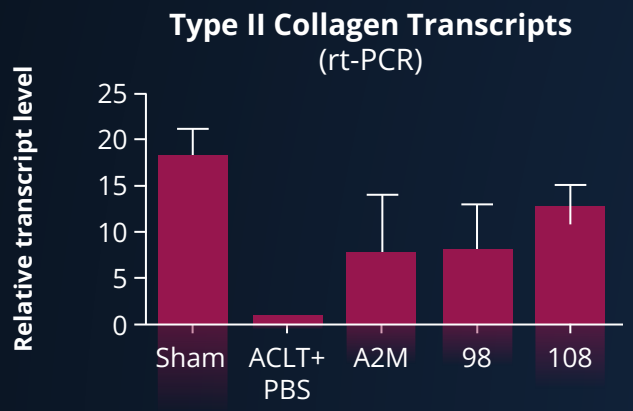
# **Collagen** in cartilage quantified by rt-PCR and IHC

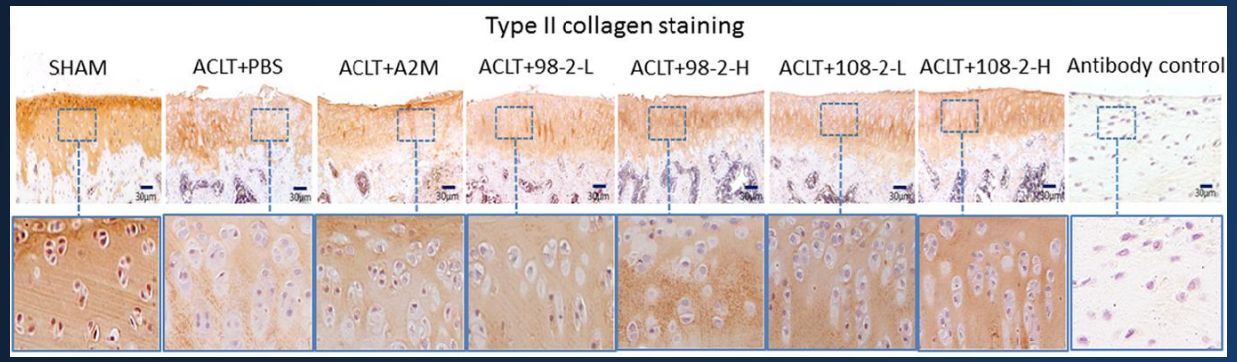
How do our A2M variants affect the **protein composition** of cartilage tissue compared to wt-A2M?




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



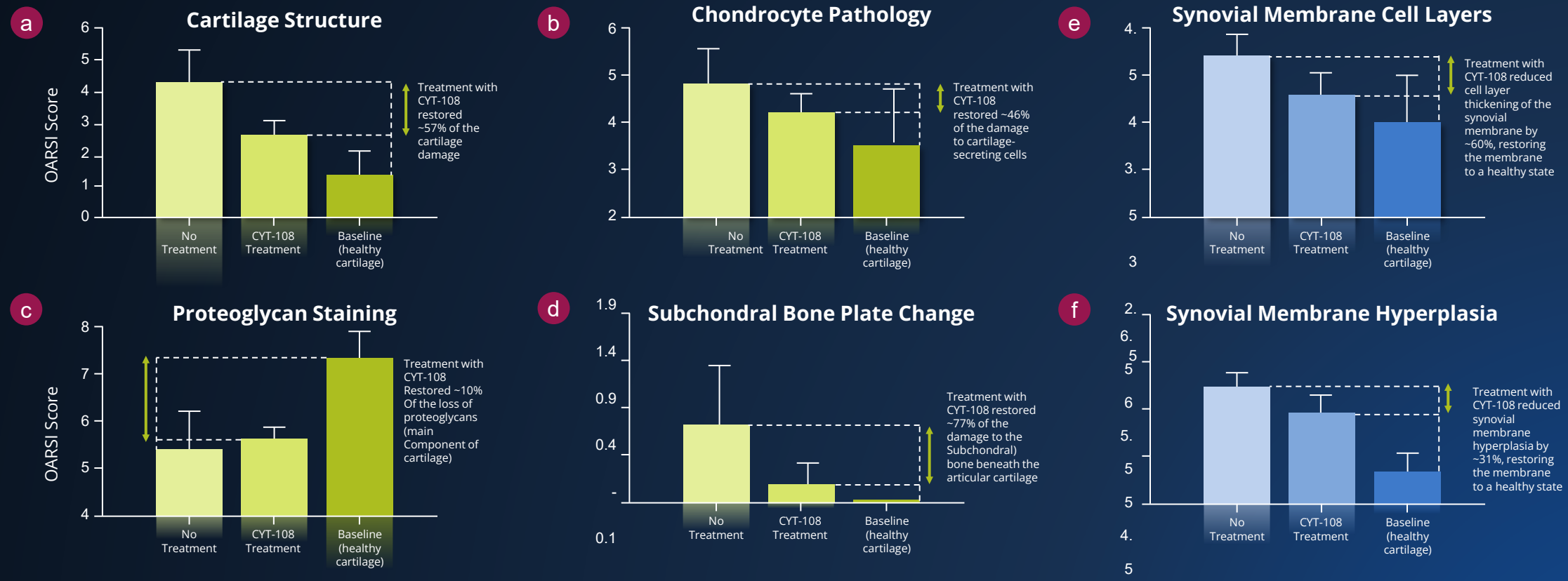

**Type II Collagen** associated with normal chondrocyte physiology and healthy cartilage
*Darker = Good*



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

# 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 cartilate 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 Safrinin-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 place (bone underneath the cartlage) thinkness 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, helathy anatomy and physiology. *Error bars+/- SEM.*