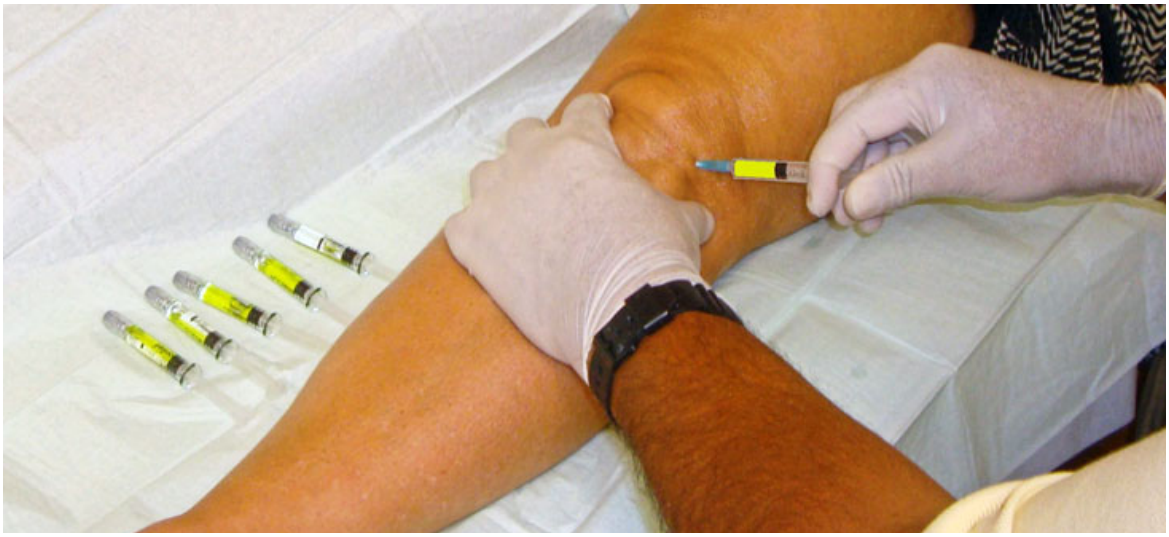

Source: Wikimedia Commons and Harry Gouvas

FINDING THE REPLACEMENT FOR HA INJECTIONS IN THE KNEE

Jeff White • Wed, July 30th, 2014

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Roughly one year ago, the American Academy of Orthopaedic Surgeons (AAOS) issued its second Clinical Practice Guidelines (CPG) reversing a long standing position with regards to viscosupplementation injections in the knee. The new CPG, which had input from the American College of Rheumatology, the American Academy of Family Practice and the American Physical Therapy Association, said the following (reference: http://www.aaos.org/news/aaosnow/jun13/cover1.asp):

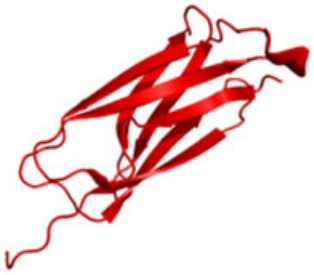
> "We cannot recommend using hyaluronic acid (HA) for patients with symptomatic OA [osteoarthritis] of the knee."
>
> "The work group understands the potential impact that this recommendation could have on clinical practice. Nonetheless, the CPG's best evidence synthesis does not support the efficacy of viscosupplementation. Although statistically significant outcomes were seen in some studies with higher molecular weight HA preparations, these outcomes were not clinically significant, based on a lack of minimum clinically important improvement (MCII)."

In January 2014 Blue Cross Blue Shield of Massachusetts announced that effective July 1, it would no longer reimburse for certain viscosupplementation products and cited the revised AAOS clinical practice guidelines. Other payers have followed suit.

If There's No HA, What Then?

While HA is still available and remains mostly reimbursable, clinicians are already asking about alternatives to HA like, for example, PRP—which recently had a strong positive study from Dr. Brian Cole's lab at Rush University.

Equally impressive is another recently published research paper—this one from Brown University which tested a therapeutic agent that, in the study, seemed to inhibit the progression of posttraumatic OA.



Crystal Structure, A2M Manomer / Source: Protein Data Bank 2P9R

The subject was something called Alpha-2-Macroglobulin ("α2M" or "A2M"). A2M is a very large plasma protein found in blood. It's synthesized mainly in the liver. But what made it interesting to the Brown researchers is that A2M is also a powerful protease inhibitor. And, as the researchers learned when they tested it, it can inhibit a broad spectrum of catabolic proteases. And what, you might ask, is the point of that? The point is that it could well be highly effective in treating one of the most pervasive and resistant chronic diseases—osteoarthritis.

Simple Experiments…Chondroprotective Implications

Brown University Campus / Source: Brown University

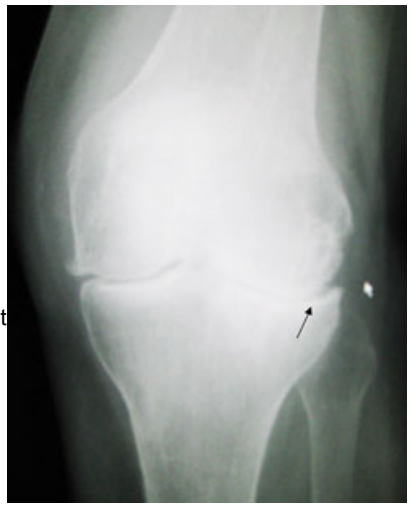
Led by Dr. Shaowei Wang and Dr. Lei Wei, **Associate Professor of Orthopaedics (Research) at the** Warren Alpert Medical School of Brown University, and joined by investigators the University Hospitals in Hong Kong and Taiyuan, Shanxi, China, the scientists ran a series of experiments to uncover the role of A2M as a chondroprotective agent in a model (rat) of osteoarthritis.

The paper titled: "Identification of α2-Macroglobulin as a Master Inhibitor of Cartilage-Degrading Factors That Attenuates the Progression of Posttraumatic Osteoarthritis" was published in the July 2014 issue of *Arthritis Rheumatology*. (*Arthritis Rheumatology* 2014 Jul;66(7):1843-53. doi: 10.1002/art.38576).

Here were their conclusions:

- A2M exists in the serum and synovial fluid in normal and in OA subjects, but levels are lower in synovial fluid;
- MMP-13 (a well-known cartilage catabolic protease associated with OA) exists in serum and synovial fluid in OA subjects, but levels were higher in synovial fluid;
- in a human chondrocytes in vitromodel, A2M inhibited the induction of MMP-13 by IL-1 in a dose-dependent manner;
- in the well-known rat model of ACL [anterior cruciate ligament] transection-induced OA, supplemental intraarticular injection of A2M reduced the synovial fluid concentration of MMP-13 **and** had a favorable effect on OA-related gene expression and attenuated OA progression.

Bottom line, said Wang et al.: **"supplemental intraarticular A2M provides chondral protection in posttraumatic OA."**



X-Ray evidence of osteoarthritis in the knee / Source: Wikimedia Commons and Ogrebot

But that wasn't all. The authors further concluded that even though A2M is present in the synovial fluid, the concentrations are not high enough to inactivate the elevated levels of catabolic agents found in OA subjects. **Adding exogenous A2M did precisely that**.

Thus, in this study, Wang et al. show that the broad-based protease inhibitor A2M is an excellent candidate for a molecular based treatment that slows the progression of posttraumatic OA.

The Other Guys Who Are Also Thinking Proteinase Inhibitor

Jupiter, Florida-based Cytonics Corporation, founded by Guy Scuderi, M.D. in 2006, has been developing a unique proteinase inhibitor approach to the cartilage degenerative process and associated pain.

As luck would have it, they were also investigating the therapeutic potential of A2M.

Some years ago, Scuderi and his team at Cytonics discovered that fibronectin-aggrecan complex (FAC), a

breakdown product of cartilage degeneration in joints and spine, is present in painful joints and discs **BUT** absent in asymptomatic joints or spine.

In 13 published papers in *JBJS*, *Spine*, and other notable journals, FAC has been shown to be a highly effective and objective biomarker for pain. (See “Dr.Scuderi’s Incredible Journey from Crash Victim to Visionary,” *OTW*, Feb 2013). Cytonics researchers believe that FAC is not just a byproduct but is in fact a mediator in the cartilage degeneration process.

What if, they wondered, there was an agent which could prevent the proteolytic cleavage of aggrecan and thereby inhibit the formation of FAC? Would that not be an effective treatment for pain and may even attenuate the progression of OA?

Their chosen agent—A2M.

A2M

In recent years, Cytonics has demonstrated A2M’s ability to inhibit MMPs, ADAMTs and all other catabolic proteases and enzymes known to be associated with OA cartilage degeneration. At Orthopaedic Research Society (ORS) in 2013, Dr. Vanessa Gabrovsky Cuellar from NYU Hospital for Joint Disease (NYU-HJD) presented Cytonics’ findings that A2M is an effective chondroprotective agent in her paper, *“*Is There a Chondroprotective Effect of Autologous Protease Inhibitor Concentrate on an Osteoarthritis Rabbit Model? A Pilot Study”.Cytonics also exhibited a poster at ORS entitled “Chondroprotective Effect of Alpha-2-Macroglobulin (A2M) on Bovine Cartilage Explants”.

In short, Cytonics arrived at A2M as a possible pain treatment and then realized it could be more than that. Wang and Wei’s team, on the other hand started with a hypothesis—which they demonstrated to be true—that A2M could actually impact progression of the disease itself in post-traumatic OA. A single treatment for BOTH the pain AND the disease itself?

ONE Treatment for Both Pain and OA

Cytonics has been quietly constructing an ark of research, intellectual property and regulatory approvals that it believes will firmly establish that A2M can effectively treat degenerative cartilage-related and other diseases…and that it has cornered the market on its use in these and other indications.

Cytonics’ first therapy is an autologous platelet rich plasma (PRP) product dubbed “APIC” (Autologous Platelet-Integrated Concentrate).

In January 2014 the company received 510(k) clearance to market APIC (BK130060) under the standard PRP indication for use. Among Cytonics’ publications is a paper demonstrating that WBCs [white blood cells], (concentrated along with platelets in many PRP products on the market today) are harmful when injected intra-articularly: Platelet-Rich Plasma Increases Matrix Metalloproteases in Cultures of Human Synovial Fibroblasts; Shawn R. Browning, Ph.D.; Amiee M. Weiser, MS; Naruewan Woolf, BS; S. Raymond Golish, M.D., Ph.D.; Thomas P. SanGiovanni, M.D.; Gaetano J. Scuderi, M.D.; Carolina Carballo, B.S.; Lewis S. Hanna, Ph.D. *J Bone Joint Surg Am*, 2012 Dec 05;94(23):e172.

Stemming from this research, Cytonics developed a unique centrifugation plus filtration process to produce a high platelet/low WBC PRP. The filtration step also has the added effect of concentrating some of the larger molecular weight plasma components including A2M.

Cheerleading Wang and Wei

Wang and Wei’s paper on A2M quite coincidentally dovetails with Cytonic’s work. The company has no relation to the Brown University researchers but nonetheless touted that work as “fully validating our years of research” — Gaetano Scuderi, M.D., a fellowship-trained spine surgeon, founder and president of Cytonics. Scuderi went on to say; “Drs. Wang and Wei’s teams have produced an elegant, elaborate and conclusive study that independently confirms our own research results showing that A2M is an important and accessible inhibitor of the catabolic proteases long known to be associated with degenerative OA. We congratulate them on the high quality of their work and their efforts in drawing attention to this exciting new treatment opportunity.”

OK, But Will Clinicians Ever See It?

Yes—FDA willing and the creek don't rise.

Gaetano Scuderi, M.D. / President of Cytonics Corp.

Independent clinicians ***unaffiliated with Cytonics*** have reported impressive results from their use of APIC in joints. Additionally, a group of VA hospital clinicians recently received IDE [investigational device exemption] approval for a study where patients would receive APIC injections in the knee joint with cytokines, lipids and mesenchymal stem cell levels tracked in the synovial fluid. The researchers plan to link these findings to outcomes measures, radiographs and cartilage characterization over six months.

Cytonics' regulatory and commercialization plan is to follow a BLA [*Biologics License Application]* regulatory route for a version of APIC that highly concentrates A2M and is void of all platelets and WBC's "APIC-CF" (Cell Free). The FDA has recently approved Cytonics' IND [investigational new drug] application for a combined Phase I/Phase II clinical trial of APIC-CF for the treatment of mild to moderate OA in the knee.

Cytonics is planning to start their 300 patient, 12-month (HA PMA-similar) study later this year.

An Off-The-Shelf A2M

Cytonics, ultimately, would like to offer an off-the-shelf A2M and pharmacologic "A2M-similar" products to treat a variety of chronic orthopedic and other diseases without the need for point-of-care preparation.

Since 2012, Cytonics has been producing A2M using recombinant protein expression technology. By slightly modifying the A2M DNA, Cytonics' researchers have engineered, produced, and tested over 150 recombinant variants of A2M, a number of which have been shown to be 4 to 5 times more effective than the wild-type A2M at inhibiting proteases that cause cartilage degradation.

U.S. and international patents have been filed for the high efficacy A2M variants as well as Cytonics process for optimizing A2M for inhibiting specific proteases.

Need Money: Will Work for FDA Approval

In the meantime, Cytonics needs money. Maybe even a strategic partner. "We are an R&D company, not a marketing firm," says Scuderi. "Our discoveries and preliminary regulatory work have set the table for what we believe will be an important new direction in the treatment of OA and degenerative cartilage diseases. We now need a big ortho or pharmaceutical industry partner to pick up the baton and move APIC and our other A2M products the rest of the way into the clinic and the market."

Source: Wikimedia Commons and Herostratus

As for Drs. Wang, Wei and team, their work is not done. Says Dr. Wei, "I believe posttraumatic OA represents only about 20-25% of knee and hip OA, while in ankle it is about 80%. Our next step will be to evaluate A2M in our model for primary OA to determine whether we think it has a similar effect."

Stay tuned, for sure.

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