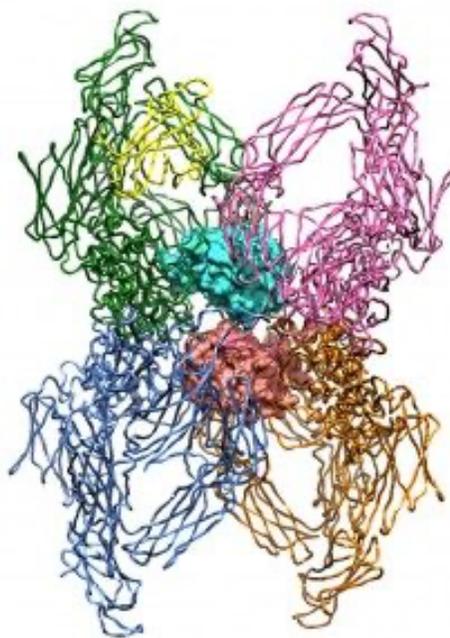


Plasma Treatment for Knee Osteoarthritis

Alpha-2-macroglobulin (A2M) is the biologic treatment for your arthritic knee that you are carrying around in your own bloodstream! It's true! Your body creates a very large protein in your liver which is carried via your bloodstream to your various organs and has several important roles to keep you healthy. The protein is called alpha-2-macroglobulin (**A2M**) and is among the largest and heaviest proteins that your body makes. It is a naturally occurring plasma glycoprotein whose principal activity is to counteract the protein/enzymes called proteases that breakdown various chemicals and molecules no longer needed in your body in a well-balanced chain of events that keeps you healthy.

In a tremendous breakthrough, scientists at the [Cytonics, Corp.](#) have discovered that this very large protein can capture and neutralize the proteases created in an arthritic joint that cause the destruction of the articular cartilage. By reducing these destructive substances, it effectively halts the progressive damage seen and felt in the osteoarthritic joint. For those of us involved in the care of the arthritic patient, this is really a huge advancement!

Before explaining this wonderful new treatment further, let's first put the problem of osteoarthritis (OA) into perspective. The Centers for Disease Control estimates that some 27 million adult Americans are afflicted with osteoarthritis. Furthermore, it is estimated that 1 in 2 adults will get symptomatic knee osteoarthritis in their lifetime. With the combination of the aging Baby Boomer population, increased longevity of U.S. citizens, and the obesity epidemic, the rising prevalence of OA is expected to contribute even more heavily to the severe health and economic effects already present. Osteoarthritis often causes weakness and disability, interferes with work productivity, and often results, ultimately, in joint replacement.



*Crystal structure of alpha-2-macroglobulin
(Artist rendering)*

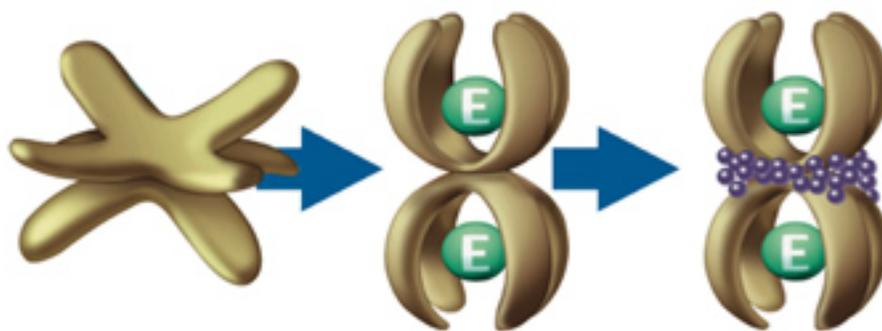
Disappointingly, we currently only have treatments that try to alleviate the pain symptoms of osteoarthritis.....NSAIDs, aspirin, Tylenol®, cortisone injections, viscosupplementation (Synvisc®), and so on. None of these treatments is actually disease-altering or what we would think of as a “biologic treatment” of osteoarthritis. In addition, we encourage weight loss, exercise, and activity modifications to deal with the fluctuation of arthritic pain that occurs in our joints.



Severe OA in knee at surgery. Complete destruction of articular cartilage.

What we have not had available so far is a true biologic treatment that alters the course of eventual destruction of the arthritic joint. A treatment that actually halts the progression of deterioration of the articular cartilage, which when finally worn completely away leaves us with little to do but to consider a surgical solution such as joint replacement surgery. What we have been looking for is a true biologic treatment of osteoarthritis that effectively stops the deterioration of the joint. We have found it in alpha-2-macroglobulin!

Not to get into the weeds too far on the biology of osteoarthritis, but it is necessary to understand, at least superficially, the process of osteoarthritis which, as we in the scientific field understand, involves a process of “turning on” or up-regulation of various catabolic (destructive) and inflammatory proteins called proteases. This up-regulation process results in a massive production of these highly destructive proteases which directly damage the articular cartilage. How the destructive process is “turned on” remains unsolved, but the collection of these proteases, including cytokines, disintegrins, and matrix metalloproteinases, are intensely destructive and over time, if unchecked, will lead to the loss of the protective cartilage covering of the joint and the development of significant and limiting joint pain.



A2M has two binding sites to which proteases are captured. This interaction permanently changes the shape of the A2M and creates a condition where the complex can now be broken down and eliminated by the body through natural mechanisms.

Circling back around, some very clever scientists have made the connection that A2M has unique and almost miraculous properties, which include a powerful inhibition of cartilage catabolic and inflammatory proteases, effectively neutralizing the process that leads to osteoarthritic cartilage degradation and joint destruction.^{1,2} In other words, it stops arthritis in its track!

In addition, another recent study from Brown University has tagged this protein as a “Master Inhibitor” of cartilage-degrading enzymes and proved that it acts not only by blocking activity of the destructive proteases, it actually suppresses gene expression that leads to elevated protease levels in the joint³. The conclusion of this study was that A2M is chondroprotective if present in high enough quantity.

Therefore, it has been inferred that supplemental intra-articular injections of alpha-2-macroglobulin diminishes cartilage degeneration and may be a potential therapy for osteoarthritis. In short, if it was possible to get more of this protein into an arthritic joint early in the arthritic destructive process, it is quite possible to at least slow, if not halt, the progression of joint deterioration.^{3,4} This would be the first truly biologic treatment for a condition that has plagued humanity since antiquity — a truly giant leap forward!

As you read above, your liver actually makes a significant quantity of alpha-2-macroglobulin and it circulates in your blood stream in a reasonably high quantity. So now, you may be thinking well why doesn't this protein just end up in the joint and help out? And this would be great...if it could. Unfortunately, studies have shown that A2M is just too darn big of a molecule to cross over into your joint in sufficient quantities to effectively neutralize those destructive catabolic proteins that have been up-regulated (“turned on”) and are destroying your joint.⁵ If only there was some way to get this miraculous protein from your blood stream into your arthritic knee. Now that would be a real breakthrough in treating arthritis.

Well, happy days! The scientists at the [Cytonics, Corp.](#) have been spending years trying to develop a method of collecting alpha-2-macroglobulin from the bloodstream and providing a relatively simple mechanism of delivering it into your arthritic knee. Just recently, they have perfected a method whereby your own blood is collected and processed with a centrifuge and a proprietary filter which isolates and concentrates your own blood product down to a small portion of highly concentrated A2M that can be directly injected into your knee or any other osteoarthritic joint.

This proprietary process from Cytonics has been named the “Autologous Platelet Integrated Concentration System” or “APIC PRP” system. It is the only PRP system currently available that concentrates A2M while minimizing platelets, white blood cells, and other proteins. All of the other PRP systems on the market leave in a high concentration of platelets and white blood cells in their preparations. This novel preparation technique is particularly important as platelets and white cells are intensely inflammatory in nature and are destructive to the articular cartilage. Again, the “APIC



Cytonics' Ultra-Filtration process to concentrate A2M from patient's blood.

PRP” system reduces the white cell count in the preparation to negligible levels, thereby allowing the concentrated alpha-2-macroglobulin to more efficiently neutralize the cytokines, disintegrins, and metalloproteinases destroying the joint. This proprietary method concentrates the A2M to a level 9 to 10 times the concentration found in the bloodstream.⁴

The “APIC PRP” system received 510(k) clearance from the FDA for use in humans in early 2014. The initiation of clinical trials with alpha-2-macroglobulin has been approved by the FDA.⁸ This marks the beginning of the era of targeted osteoarthritis therapy with enhanced versions of A2M currently in development.⁹

In the first roll-out to the public, the Cytonics, Corp. is allowing only **selected physicians** access to their proprietary process. Fortunately, Dr. Zehr is one of the **selected physicians** and we are doing the “APIC PRP” procedure at the Zehr Center for Orthopaedics! We have chosen to name this procedure, when done at our office, The PLATELET PLASMA “PLUS” or the “PPP” shot for osteoarthritis of your knee to signify that it is in the FDA-designated category of Platelet Rich Plasma but is truly more of a specialized protein “PLUS” injection. Again, this is truly unique among the others of this classification.

A few words of note!!!

- This biologic treatment works best in joints where the destruction has not reached the point of total destruction, or where the joint is “bone on bone.” This is referred to as “end stage arthritis.” A biologic treatment that is designed to help “slow” or “prevent” further destruction will have little effect when the destruction of the articular cartilage has become extreme. This would be analogous to calling the fire department after your house has burned down. This treatment is FDA-approved for the treatment of mild to moderate osteoarthritis.
- This new treatment is not the “platelet rich plasma” or “PRP” concept that has been available through many companies for over a decade and is typically used in the sports field and for tendon injuries. In fact, a high concentration of platelets is quite inflammatory to a joint and will not be beneficial. Several studies and the American Academy of Orthopaedic Surgeons have recommended *against* the use of “PRP” in osteoarthritic joints, describing it as not helpful or flat out useless.^{6,7} The “APIC PRP” system referred to here minimizes platelet and white cell concentrations while maximizing the concentration of the desired chondroprotective protein alpha-2-macroglobulin. This is wholly unique in the populated field of PRP systems currently available.
- Payment of A2M is NOT covered by Medicare, nor by the typical commercial insurers. As a result it will need to be paid for like a supplemental treatment. As a note, PRP is not covered by these insurers currently, nor are most of the viscosupplementation treatments.

If this cutting edge therapy appeals to you, contact our office directly to set up an appointment to see if you are a candidate for this unique and “tip of the spear” biologic treatment of your arthritic knee joint.

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