

## **Alpha 2 Macroglobulin: The Age of Targeted Therapy for Osteoarthritis Begins**

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*Thanks to the work of the visionary surgeon-scientist Gaetano Scuderi, MD, his team at Cytonics Corporation, and other researchers around the world, alpha 2 macroglobulin soon may revolutionize the treatment of osteoarthritis.*

In 2005, a fellowship-trained spine surgeon named Guy Scuderi was accelerating up a ramp on to I-95 when a pedestrian strolled on to the interstate ramp. To avoid the pedestrian, Scuderi maneuvered his motorcycle, and in the process, lost the skin on his hands, the bone of his right kneecap, and tragically, the future of his career as an orthopedic surgeon.<sup>1</sup>

During the following year, Scuderi experienced pain and underwent multiple surgeries. In the process, Dr. Scuderi began to wonder where pain is located in the body, and was inspired to search for better ways to treat the condition.<sup>1</sup>

In an interview, Dr. Scuderi stated, “I started looking at joint disease and pain about 10 years ago, and I identified a protein called the FAC, or fibronectin–aggrecan complex, that was synonymous with pain following a joint injury.” For Dr. Scuderi, research on levels of FAC was the beginning of a search for the master pain regulator of joint pain.

Scuderi found that FAC was present in high levels in synovial joints that had been damaged by osteoarthritis. For instance, in the hip synovial fluid of 34 patients with arthritis undergoing surgery, investigators measured levels of inflammatory markers before performing the surgical interventions. Scuderi and colleagues measured standard cytokines (of which there are 12), and an additional marker: FAC.<sup>2</sup>

In the study, FAC was the only biomarker significantly associated with the severity of osteoarthritis. FAC, which is a byproduct of cartilage breakdown, is a predictor of hip pain.<sup>2</sup> Researchers identified similar relationships between FAC levels and the severity of knee, ankle, and spinal damage.<sup>2-7</sup>

Beyond this association, FAC levels were predictive of outcomes in patients undergoing lumbar discectomy. In a series of 92 patients, high levels of FAC were a positive predictor of clinical improvement three months after surgery, with 85% positive predictive value.<sup>7</sup>

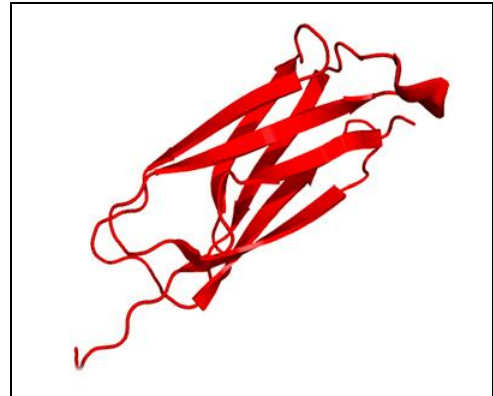
Having identified a reliable biomarker associated with pain and inflammation, the next step was to use information about FAC to find out how the body heals and relieves pain. Dr. Scuderi already knew that the body has significant capacity for healing itself. In the pursuit of that intrinsic healing factor, Dr. Scuderi needed funding. According to Scuderi, “a company called Synthes Corporation became interested in what I was doing and they invested \$9.5 million in the company.”

With this infusion of funding, Scuderi formed a research firm called Cytonics Corporation and was able to investigate the components of the body associated with reducing levels of FAC and

reducing pain. “I started investigating fractions of blood...I felt that there are lots of patients who seem to get better on their own who seem to get better on their own.”

Eventually Dr. Scuderi and researchers at Cytonics found the factor that helped some patients reduce levels of FAC and the pain and inflammation associated with high levels of FAC. That protein was alpha 2 macroglobulin (A2M).

Scuderi’s team at Cytonics discovered that A2M worked on three classes of proteases that degrade cartilage cells or chondrocytes. These proteases include cytokines (TNF alpha, and interleukin 1), matrix metalloproteases (MMPs), and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs).



Alpha 2 macroglobulin protein.  
Courtesy of Wikimedia Commons.

“Only alpha 2 macroglobulin can stop all three,” said Scuderi.

Dr. Scuderi had found the master pain regulator, but because A2M is present in nature, it could not be patented and developed as a medication. To develop A2M commercially, Dr. Scuderi needed to alter A2M in a way that would improve its bioactivity, so Dr. Scuderi turned to his research team at Cytonics. According to Scuderi, “Of 180 variants we built ... we made four that were better [than the natural product], and secured a patent on alpha 2 macroglobulin in 2009 through 2010.”

The form of A2M that Dr. Scuderi and his team developed was substantially better than the natural protein. Scuderi concluded, “We modified it and were able to enhance its activity up to about 400% or 500%.”

Dr. Scuderi and his team at Cytonics were hard at work developing A2M when a team of researchers at Brown University independently identified the same master regulator of inflammation and pain that Dr. Scuderi and his team had identified and had been developing for years.<sup>8</sup>

Unlike the researchers at Brown, however, the team at Cytonics has already progressed far beyond the basic research phase. According to Scuderi, “We built a system that concentrates both platelets and alpha 2 macroglobulin.” This system removes, “almost all the white cells, all the red cells, most platelets and most of the other proteins.” In this way, Scuderi and his team can purify a patient’s own natural alpha 2 macroglobulin, and inject the super concentrated A2M into joints. So far, approximately 200 patients have received this autologous treatment.

According to Scuderi, “The success has been phenomenal. I can take your pain away in 24 hours...[and] stop cartilage degradation in its tracks.” The autologous A2M treatment, which is derived from two milliliters of whole blood, and administered two to three times per year, in some patients, has led to “four to five months of complete pain relief.” Clinical trials with autologous A2M are underway (see ClinicalTrials.gov entry NCT01613833).<sup>9</sup>

Meanwhile, the recombinant form of A2M protein, which has several times the activity of the natural protein, is still in laboratory development, although development continues rapidly. Scuderi expects to complete development of the recombinant protein, “in the fourth quarter of this year [2014].”

*Patients of Dr. Scuderi are already receiving treatment with A2M therapy at his office in Jupiter, Florida. Other nearby orthopedic specialists in Florida are offering the treatment, as well. One such office is the Zehr Center for Orthopaedics in Naples, Florida, where Robert J. Zehr, MD, offers the treatment for some patients.*

*In an e-mail exchange, Dr. Zehr noted that he is using A2M therapy in only in patients with knee arthritis, “who would otherwise be candidates for knee replacement surgery.” In addition, for now, Dr. Zehr confines the conversation about A2M therapy to patients who “have tried the more conventional treatments but are still reluctant to pursue surgery.” Of the six treatments with A2M Dr. Zehr has administered, including treating his own knee, Zehr noted, “five patients are satisfied that the treatment is helping and one, unfortunately, gave up quickly and proceeded to total knee replacement.”*

*It should be noted that autologous A2M replacement, according to Zehr, “is not covered by insurance or Medicare.” Despite barrier of reimbursement, Zehr remains enthusiastic about A2M therapy, which, according to Zehr, “represents the first true biologic treatment of osteoarthritis by addressing the actual destructive proteins that attack the articular cartilage and support collagen in our joints.”*

The Food and Drug Administration has also shown exuberance with regard to early trials of the A2M therapy. In a press release published on July 22, 2014 by Market Watch, Dr. Scuderi spoke about the initiation of a phase I/II clinical trial using Cytonics Corporation’s APIC cell-free system noted, “This approval by the FDA, 30 days after our initial submission and with no iterative rounds of review, is a testament to the comprehensive and high quality work that our team has executed.” Scuderi continued, “Cytonics' accomplishments in the scientific, intellectual property, regulatory, and now clinical aspects of A2M have positioned Cytonics to bring this important new molecular treatment for degenerative cartilage to the clinic and the market.”<sup>10</sup>

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