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DMS Biotech osteoarthrosis project: a simple, inexpensive and efficient response to a non-satisfied medical need

DMS Biotech, division of **Diagnostic Medical Systems Group (Euronext Paris - FR0012202497 - DGM)** dedicated to biotechnologies and specialized in the development of innovative technical solutions for the use of adipose tissue in medicine, details its development strategy for its technologies related to the treatment of osteoarthritis and regenerative medicine based on the injection of adipose-derived stem cells, following the positive results of the clinical trial in the osteoarthritis treatment of the knee.

Osteoarthritis: a recognized public health issue

Osteoarthritis is the main threat for joints and is, therefore, a real public health issue. Between 9 and 10 million cases were referenced, in France only. 65% of the population over 65 are affected, inducing a particularly important economic cost for the local authority (14 million prescriptions and 300 000 X-ray examinations). This situation is equivalent in every developed country.

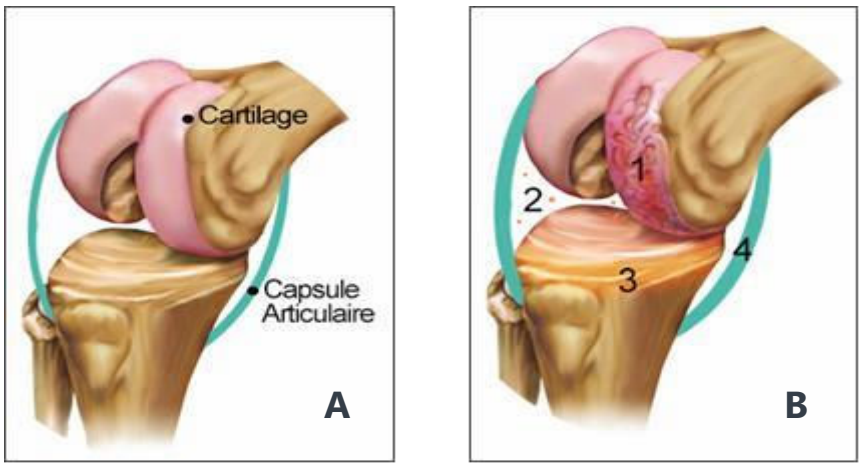
All joints can be affected. However, shoulders, elbows, wrists and ankles are less likely to be concerned. The frequency of the disease depends on the location:

- **Osteoarthritis of the spine** is the most frequent for people between 65 and 75 (70% to 75% of affected people) but remains most of the time clinically silent, so painless;
- **Fingers osteoarthritis** is the second most frequent (60%) and results in distortions, most of the time irreversible and very invalidating;
- **Osteoarthritis of the knee and the hip** affects respectively 30% and 10% of people between 65 and 75. They are also very invalidating because they reduce massively the mobility of affected people.

Cartilage lines the bone extremities of joints and allows their optimal relative sliding. Osteoarthritis is characterized by cartilage destruction; it loses its thickness, cracks apart and finally disappears. However, it is now established that osteoarthritis does not only damage cartilage, the other parts of the joint are also concerned. As illustrated on figure 1 below, there is an inflammation of the synovial membrane and a thickening of the joint capsule, a modification of the synovial liquid composition with calcifications, sclerosis and a remodeling of the subchondral bone.

The cause of osteoarthritis is therefore an overall damage to the joint.

Figure 1: schematics of a sane joint (A) and a joint with osteoarthritis (B)



1: destruction of hyaline cartilage
2: calcification in the synovial liquid
3: sclerosis of the subchondral bone
4: thickening of the joint capsule

Osteoarthritis: a non-satisfied medical need considering the absence of etiological treatment

Currently, there is little understanding of this degradation's mechanisms. The causes are multifactorial and therefore difficult to understand or identify. It is currently established that, in osteoarthritis, the activity of chondrocytes (cartilage-making cells) is disturbed and leads to the excessive activation of catabolic enzymes of the matrix, called metalloproteases, that will damage the cartilage.

This ignorance of osteoarthritis causes, explains the fact that, to this day, no etiological treatment, which means allowing recovery, has been found. No recent discovery has been made to consider a therapeutic strategy of curative treatment. Only symptomatic treatments, aiming to ease the inflammation and/or the pain, have been developed so far.

Indeed, osteoarthritis translates into inflammation and pain, although there is a dissociation between the symptoms and severity of the joint's damage. In any case, these damages lead to a decrease of mobility stimulating the progression of the pathology. Indeed, a lower motor function will cause the melting of the joint's stabilizing structures (muscles and tendons) leading to a joint laxity that is allowing rotational movements in unusual axes. These inappropriate sliding movements will induce a cartilage damage increasing the pain and further preventing the patient from moving. This auto-amplifying vicious circle leads to the installation of the pathology from which the patient won't be able to recover and that will translate into chronic phases: daily discomfort remaining moderate and manageable and intense painful crises with an important inflammation. To manage these situations clinically, several types of treatments of knee osteoarthritis are currently used.

- **Viscoelastic gels** can be injected in the joint to reduce the restrictions and the frictions between the cartilage parts inducing pain (technique called viscosupplementation). The most familiar product is hyaluronic acid. Its therapeutic action is low and limited in time. In addition, its low efficiency led the HAS (French National Authority for Health) to stop reimbursing this type of treatments;

- **The analgesics** are prescribed to deal with pain. The main one is paracetamol, but other molecules are available and adapted to different pain thresholds. the analgesic molecules, although efficient, have significant adverse effects such a hepatic and renal toxicity, making it necessary to limit its dosage;
- **The nonsteroidal (NSAID) and steroidal anti-inflammatory drugs,** administered orally or as a gel or even as an injection, are used to reduce the inflammation. In the case of major inflammatory eruptions, a corticosteroid injection is often recommended. It consists in injecting powerful steroid anti-inflammatory drugs directly in the joint. But glucocorticoids are toxic for chondrocytes and therefore cartilage, limiting the number of injections to three per year for the same joint;
- **Blood platelets**, known for many years, they can secrete many molecules after an activation. The products using this secretory source are called PRP (Platelets Rich Plasma). The studies using this product seem contradictory, and the possible positive effects seem short-lived.

Thus, no conventional treatment provides a therapeutic satisfaction, especially in terms of duration and efficiency, requiring a frequent renewal of the treatment inducing in some cases, toxicity risks and significant costs for the care of the patient.

New molecules are being developed or in clinical trial, and many teams try to develop non-pharmacological innovative therapeutic approaches in order to overcome these disadvantages. Most of them choose cell therapy through the use of Mesenchymal Stem Cells (MSC). These cells are able to self-renew and to differ in several cell types especially in chondrocytes.
Almost all tissue in the organism have mesenchymal stem cells. However, the adipose tissue represents the main source used clinically because MSC are abundant and liposuction is an easy and minimally invasive way to reach them.

Osteoarthritis: the cell therapy solution

To treat osteoarthritis, two strategies using MSC are available:

- The first strategy consists in using the differentiation capacities of the MSC in chondrocytes and in injecting the differentiated cells in the joint. The goal is to produce cartilage in order to fill in the damaged areas in the affected joint. The cells are often coupled to a biomaterial allowing injected chondrocytes to join and multiply optimally. Some research teams pushed this theory as far as possible by trying to develop in vitro cartilage, cultivating chondrocytes in order to make implants allowing the partial or full reconstruction of a damaged joint. But these techniques will require many years of research and development before becoming efficient on the therapeutic level. Considering the technical challenges, no one can be sure this strategy will lead to success;
- The second strategy consists in using MSC's secretory capacities. Indeed, they are able to secrete growth factors and anti-inflammatory molecules. Growth factors stimulate the endogenous stem cells in the joint to produce cartilage. The anti-inflammatory molecules allow to stop the cartilage-damaging inflammation during intense outbreaks of the disease and therefore to stop cartilage erosion.

Several studies based on the injection of MSC after being purified by cell culture have been or are being conducted. The ADIPOA 2 program, conducted by professor Christian Jorgensen (university hospital of Montpellier) and professor Frank Barry (Galway, Ireland), started in late 2015 for a multicentric clinical trial (with Paris and Toulouse) and in 10 centers in Europe. This study was intended to include 150 patients in a randomized controlled trial (2 arms of 50 patients each with an injection of stem cells at different doses and an arm of 50 patients without stem cells injection). However, this study's protocol is based on the isolation of the MSC by collagenase tissue digestion and cell expansion by culture in laboratory.

But when reading the regulation, the procedure of culture and collagenase tissue digestion proves to be very restrictive (almost equivalent to drugs) and has many technical and financial constraints strongly hindering commercial development because the price of the treatment will be high, with no guarantee to succeed.

DMS Biotech: a simple and efficient therapeutic protocol

A pre-clinical study in dogs have been realized and the results are very positive in terms of pain and limp reduction. It gave the possibility to conduct a clinical study in human subjects, with 40 participants (see press release from May 22nd, 2019).

This study is over, and the results are currently being written for a scientific publication. The protocol allowed to reduce significantly the pain up until one year in treated osteoarthritis patients. This effect can probably last longer but the follow-up period of patients included in the study does not allow to know it.

In conclusion, the therapeutic protocol developed by DMS Biotech is simple and efficient. The procedure lasts about 30 minutes (from the adipose tissue sampling until the cell injection in the joint) and the entire procedure is performed in operating theater, under local anesthetic. In addition, this protocol will allow to avoid many sessions of post-operative rehabilitation, necessary after a knee prothesis for instance.

The implementation of the procedure is based on the use of a single-use kit with several innovative patented elements.

The proposed treatment has good tolerance without adverse effects, is performed without adding a foreign body or harmful chemical products and is effective on pain over a period of at least one year for a single injection.

The financial cost of the kit and intervention will be low, which should allow a reimbursement by the health insurance considering the cost/efficiency ratio, for the benefit of the greatest number of people.

About DMS Group

DMS Group is composed of companies with a high innovation potential. Historically centered on medical imaging, the activity develops in new directions. By investing on the future and betting on research, DMS Group hopes to bring the solutions of tomorrow.

- Specialized in high technology for medical diagnosis, **DMS Imaging** is now the French leader in development, design and manufacture of RF imaging systems dedicated to radiology, bone densitometry, 3D modeling and posturology.
- **DMS Wellness** gathers activities dedicated to health and wellness, for specialists in physiotherapy, beauty, aesthetics and sport.
- **DMS Biotech** supports the development strategy of the group in the field of biotechnologies, and more specifically, technologies for the treatment of osteoarthritis and regenerative medicine based on the injection of fat stem cells.

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Contacts

DMS Group		
Jean-Paul ANSEL	CEO	04 67 50 49 00
ACTUS FINANCE		
Mathieu OMNES	Investors relations	01 53 67 36 92
Alexandra PRISA	Press Relations	01 53 67 36 90