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Newsletter from Xintela AB No 2 2024

XSTEM® - A stem cell product with unique properties and broad therapeutic potential

In this newsletter we focus on our stem cell product XSTEM, its competitive advantages, the status of our clinical development and the broad application opportunities that XSTEM can bring to patients.

We have asked Lucienne Vonk, our new Chief Scientific Officer, to present her background and engagement in the regenerative medicine field and her perspectives on Xintela's XSTEM product platform.


Lucienne Vonk, CSO

Lucienne, what caught your interest in regenerative medicine?

Early in my career, during an internship in my undergraduate molecular biology degree, I was introduced to Tissue Engineering and Regenerative Medicine, which fascinated me. I was very fortunate that I could continue my education in this field as a PhD student on a project investigating cartilage tissue engineering at the department of Oral Cell Biology at the Academic Center for Dentistry Amsterdam, The Netherlands. Afterwards, I joined the department of Orthopaedics, University Medical Center Utrecht, The Netherlands. There, I started to focus more on cell therapies and my research shifted from fundamental research to translational and clinical research. I was part of the team that developed - from start to late phase investigator-initiated academic clinical trials - a one-stage cell therapy for focal cartilage defects using a combination of the patient's own cartilage cells and mesenchymal stromal cells from a donor. I found it very satisfying and stimulating that my research could influence and change patients' treatment and improve their lives. From 2019–2022, I headed first the Research & Development and later the Scientific Liaison departments at CO.DON AG in Germany. As they have a marketed autologous cell therapy product, I gained further experience with industry-driven clinical trials and the many different aspects that come with commercial production and the regulatory and market access processes of advanced therapy medicinal products (ATMPs). In October 2022, I joined Xintela as Director Musculoskeletal Diseases and, in February 2024, I was honored to take over the role of Chief Scientific Officer.

"I believe that Xintela's stem cell technology, based on the stem cell marker integrin α10β1, has huge advantages in the development of safe and effective allogeneic stem cell therapies." *Lucienne Vonk*

Why did you join Xintela?

I believe that Xintela's stem cell technology, based on the stem cell marker integrin α10β1, has huge advantages in the development of safe and effective allogeneic stem cell therapies. The selection of allogeneic (donated) mesenchymal stem cells (MSCs) using this marker ensures a homogenous and consistent product of high quality which can meet regulatory requirements for ATMPs and also has a great advantage for obtaining market approvals in the future. Stem cell preparations without such a selection step contain contaminating cells that can negatively affect safety and therapeutic efficacy. As the number of contaminating cells is different between different preparations, the quality of the preparations will differ as well. The MSC selection step makes XSTEM unique and that is why this product stands out from others. I also believe that the use of allogeneic (donor) cells will become the leading approach in the cell therapy field. Only with allogeneic cells it is possible to offer a true off-the-shelf cell therapy, that is easy for both the patients and the doctor, as the cells come from a donor and are not harvested from the patients themselves (autologous cells). In addition, treatment costs per patient are much lower compared to autologous cells, as several thousands of patients can be treated with stem cells from one donor. And, cells with high quality and therapeutic potential can be prepared and stored until treatment of patients.

My position at Xintela allows me to actively contribute to and work on the things I am passionate about: advancing regenerative medicine through translational and clinical studies to bring new cell therapies to the market to improve patients' lives.

Why has Xintela chosen osteoarthritis as the first in indication for XSTEM treatment?

There is a huge need for an effective treatment for osteoarthritis. More than 500 million people suffer from this disease globally and, with ageing populations and increasing rates of obesity, the prevalence of osteoarthritis is expected to increase further. Osteoarthritis is a degenerative joint disease that is characterized by progressive loss of articular cartilage and other changes in joint tissues, often combined with low-grade chronic inflammation. This causes persistent pain, loss of function, disability, and decreased quality of life. Osteoarthritis is associated with a huge economic burden to society. Current treatments for osteoarthritis are focused on improving pain and function. These treatments can be non-pharmacological, such as physiotherapy and lifestyle education, or pharmacological, such as the use of painkillers and anti-inflammatory agents. None of the current treatments has been shown to halt or reverse the progression of osteoarthritis. Joint replacements are indicated for end-stage osteoarthritis patients and recommended only for patients above 60 – 65 years of age. Although the first joint replacement is usually very successful, the implants have a limited lifespan and replacing the implant with a new one is difficult and comes with increased risk of complications and a lower success rate. Consequently, there is a large group of osteoarthritis patients who are too young for a joint replacement, who need to live with the disease, and who can only partially manage their symptoms and are often dependent on frequent use of painkillers.

Thus, there is still a high need for a treatment that can alter the natural course of osteoarthritis by stopping or even reversing structural changes in joints and improving symptoms - a so-called disease-modifying osteoarthritis drug (DMOAD).

In our preclinical studies, we have demonstrated that integrin α10β1-selected MSCs have a DMOAD effect. It was shown that XSTEM, after injection into the joint cavity, will move to the locations where there is cartilage damage, and that they can differentiate into cartilage cells and make new cartilage tissue. In addition, they also secrete factors that resolve ongoing inflammation and stimulate other cells in the joint to create a healthier micro-environment and restore tissue damage.

In addition, we have shown in horses, with our equivalent equine MSC product EQSTEM, that injection of EQSTEM into joints with post-traumatic osteoarthritis decreased pain and improved both joint function and cartilage tissue structure. Altogether, our preclinical studies demonstrate that we have a unique stem cell product that can potentially make a huge improvement in human osteoarthritis patients with its disease-modifying potential.

Tell us about the ongoing clinical study in knee OA patients

This is our first-in-human clinical study (Phase I/IIa) with XSTEM for moderate knee osteoarthritis which is ongoing in Australia. The primary goal of the study is to show that XSTEM is safe, but preliminary efficacy

signals, including DMOAD effects, are also being investigated. We have chosen knee osteoarthritis because the knee is the most frequently affected joint. Three different dose levels have been dosed in 24 patients, 8 patients per dose level. The study safety review committee has judged all three doses as safe three months after treatment. So far, there is an early trend on all dose levels, that patients experience reduced pain and improved joint function in the knee six months after the injection of XSTEM. For all patients, efficacy readings are done every six months for 18 months. We have the possibility to expand the study with an additional 30 patients and we are currently discussing the best way forward.

What about XSTEM for other indications?

XSTEM has the potential to treat many diseases, due to its ability to regenerate damaged tissues and organs, regulate the immune system, and dampen inflammation. Xintela focuses on the development of stem cell therapies for diseases where there is a high unmet medical need. Our second clinical study (Phase I/IIa) with XSTEM is currently ongoing in patients with difficult-to-heal venous leg ulcers. Venous leg ulcers are one of the most common chronic wounds and the overall prevalence is estimated to be around 4% in people above 65 years of age. They cause symptoms such as pain, itching and swelling of the affected leg and venous leg ulcer patients often present with social isolation. The first patients have been dosed in our ongoing study. In total, twelve patients will receive either XSTEM or placebo applied to the wound and thereafter safety and efficacy are evaluated weekly for ten weeks and at four months after treatment. We have previously shown, in preclinical studies, that XSTEM has an excellent wound healing capacity.

We also have strong preclinical data for the use of XSTEM in the treatment of Acute Respiratory Distress Syndrome (ARDS). This is a serious lung condition with high mortality and can be a complication from, for instance, blood poisoning, pneumonia and lung injury. Many patients died from ARDS during the covid-19 pandemic. Our preclinical results that were published in the scientific journal Respiratory Research (Edström et al., 2023) demonstrated that XSTEM, among other therapeutic effects, reduced lung tissue damage in an ARDS model.

Interestingly, the possibilities for broader uses of XSTEM do not stop there. Only in the musculoskeletal field, XSTEM can be a treatment for osteoarthritis in other joints including hand, hip and ankle, and for degenerative disc disease, large bone defects, as well as tendon and ligament pathologies. We also see other skin indications, such as skin burns, and central nervous system disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and spinal cord injury, in the coming therapeutic pipeline for XSTEM. And there is a whole range of inflammatory diseases where XSTEM holds promise. To be able to further develop and commercialize XSTEM for several indications, we have plans to enter into partnerships and to out-license XSTEM. A great competitive advantage is that we have stem cell product patents granted in several important markets including the US, Europe and Japan for all therapeutic uses of XSTEM. Another great advantage is that we produce XSTEM ourselves in our own GMP-approved facility.

Besides treatments for humans, many animals suffer from similar diseases. For instance, the abovementioned musculoskeletal diseases also frequently occur in horses and dogs. Much of our preclinical work on osteoarthritis has been performed in horses and this can also form the basis of a marketed product for horses. I do look forward to reactivating our development of stem cell products for horses and other animals, when we have a development partner on board.

Can you comment on the competition from other stem cell companies in the osteoarthritis field?

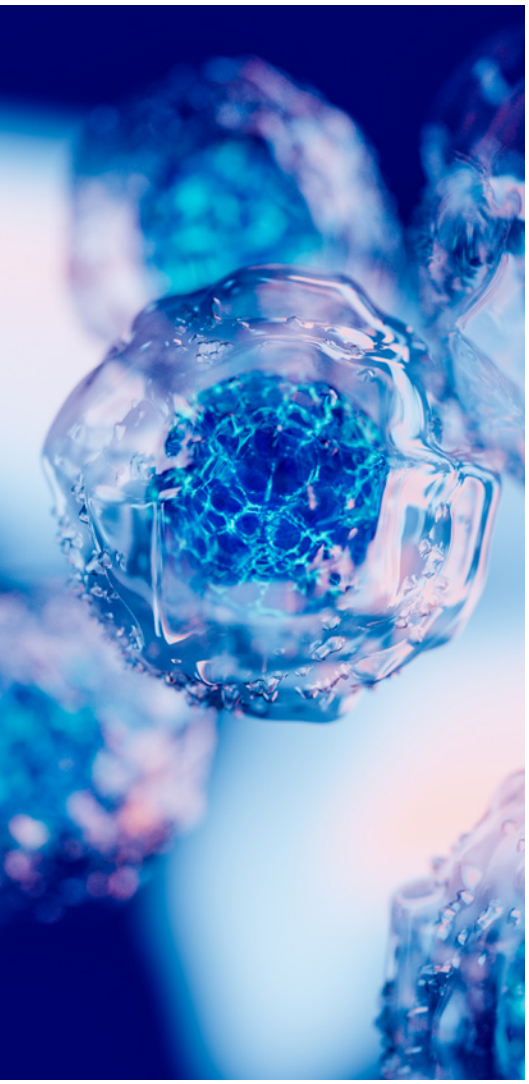
As mentioned, there is currently no approved DMOAD. However, there are several companies that have started or are planning to start late-stage Phase III studies with their cell therapy for the treatment of osteoarthritis. None of these cell therapies consist of selected MSCs.

Stempeutics (India) has published Phase III data with their allogeneic bone marrow MSCs product Stempeucel-OA (Gupta

VÄSTRA HAMNEN
CORPORATE FINANCE

"Xintela: Awaiting results in trials and discussions"

Read the Research update Q4 2023 here.



et al., Am J Sports Med. 2023). Medipost (Korea) has approval for Cartistem, an allogeneic umbilical cord blood-derived MSC product, in Korea and is currently performing a Phase III study for osteoarthritis in Japan. Magellan (Australia) planned to start a phase III study with MAG200 (allogeneic adipose MSCs) in the last quarter of 2023, as did Cellular Biomedicine Group Ltd (China) with the allogeneic adipose-derived mesenchymal progenitor cell product Allojoin in China. Another ongoing cell therapy osteoarthritis Phase III trial is by Cynata (Australia) on CYP-004, which is an induced pluripotent stem (iPS) cells-derived MSC product.

I like to emphasise that none of the above-mentioned cell therapies consist of selected homogeneous MSCs.

There are also cell-based treatments taking place in clinics that are sometimes mistakenly referred to as stem cell treatments. These treatments are with minimally manipulated tissue products, such as, concentrated bone marrow, or the stromal vascular fraction of adipose tissue. Only a very small percentage of the cells in these products are mesenchymal stem cells (0.001% - 0.01% in and bone marrow concentrate, 1 - 4% in the stromal vascular fraction of adipose tissue). These tissue products are often produced using a registered (such as CE-marked) medical device but the products themselves are not registered. The regulations around these tissue products are less strict. As the products are not drugs or medicinal products, they are usually not covered by healthcare insurance. Xintela's stem cell products are regulated as ATMPs and are required to possess proven safety and efficacy. In addition, each product is quality tested and can be covered by healthcare insurance and thereby become available for everyone.

Finally, tell us about your network and engagement in the cartilage regeneration field

I have been very active in several national and international professional societies and associations. One of those is the International Cartilage Regeneration & Joint Preservation Society (ICRS). I was the co-chair for the scientific program for the world meeting of the ICRS in 2019 in Vancouver and I have been a member of standing committees of the ICRS since 2013. Currently, I am the deputy co-chair of the translational research committee and I am Senior and Social Media Associate Editor for the official journal of the ICRS, the Journal of Cartilage & Joint Preservation. For me this is a very efficient way to play an active role in the cartilage regeneration field, to educate others and keep updated on what is ongoing in the field, to early identify upcoming trends and changes, and to be part of a global network of present and future Key Opinion Leaders (KOLs) in the field. I get regular invites to speak at a variety of international meetings. I always represent Xintela, but the presentations are not always directly related to the activities that currently occur within Xintela. For instance, last year, I gave presentations on synthetic bone grafts and ligament repair. There are not many people working at the interface between basic science and clinical care and therefore I always cover the translational aspects and address the topics in a way that is interesting and informative for both scientists and clinicians. In addition, actively participating in discussions at these meetings can be both informative, influential and important in our ambition to broaden XSTEM therapy to other musculoskeletal indications.

We look forward to a continued exciting journey with XSTEM with results from our ongoing clinical studies as well as partnerships to take XSTEM further through clinical development and to the market and to the patients.

With best regards,
Evy Lundgren-Åkerlund
CEO

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