EU Project GAMBA: New hope for osteoarthritis patients

In as little as a few decades from now a mix of stem cell and gene therapy could heal arthritic joints from within. Citizens and patients will discuss the chances and risks of this therapeutic approach with experts and scientists working on the project.

Bridget M. is having one of her bad mornings. Her left knee is hurting and she doesn't know how to get up. "The first moves and steps are always the worst" reports the 62-year-old. Her knee has been troubling her for 5 months now. At first she ignored the pain. Then her daughter persuaded her to see a doctor. Her orthopaedist examined her and Ms M. described the pains, which occur mainly after resting and improve the more she is moving. Because of these typical so-called warm-up pains the orthopaedist immediately suspected osteoarthritis. A radiological examination confirmed the suspicion and also showed that the osteoarthritis of her knee is very advanced.

In Ireland, an estimated 400,000 people (about 10 percent of the total population) are suffering from the very common illness osteoarthritis. Over time, the cushioning cartilage layer in the diseased joints becomes increasingly thinner until bone rubs on bone. The risk to develop osteoarthritis increases with age. About 9% of all 20-year-olds, 17% of all 34-year-olds and up to 90% of all over 65-year-olds are affected.

Like Bridget M. many patients don't notice the gradual joint deterioration for a long time; this deterioration is especially common in heavily used joints such as knee, hip or shoulder. Only very few patients are diagnosed in the early stages and treated with therapies, which delay the degenerative disease somewhat. Weight reduction can ease the burden on the joint and corrections of misalignments also show good results. Nevertheless it is not really possible currently to stop further cartilage degradation.

To alleviate the pain and to postpone a replacement of the joint with an artificial one, the following and other methods are used:

- Pain-causing debris is washed out of the joint
- Joint fluid replacements are injected into joints between the cartilage layers,
- Small punch holes (microfractures) are made into bones, to enable stem cells from the bone marrow to reach the joint and to recreate cartilage or bone cells
- The patient's own cartilage cells or even cartilage and bone pieces are harvested from non load-bearing parts of the joint and inserted into the diseased area.

Nevertheless, the disease progresses and the affected joint has to be replaced with an implant. This therapy enjoys good success rates if the patients cooperate fully in the rehabilitation phase.

But what if it was possible to halt cartilage degeneration and to repair bone damage? Mary Murphy and Eric Farrell, biologists at the Regenerative Medicine Institute (REMEDI), National University of Ireland Galway, are pursuing this aim. "We want to encourage the body to heal itself" explains Murphy who is responsible for the Irish part of GAMBA. Eight other research groups in Germany, France, Italy, the Netherlands and Switzerland are involved in this 3.2 million Euro EU research project GAMBA (Gene Activated Matrices for Bone and Cartilage Regeneration in Arthritis) which runs until mid 2013.

This visionary project encompasses the most up-to-date fundamental research in stem cell and gene therapy, nanomedicine and new biomaterials with the aim of finding the ideal combination of these to induce a healing from within, directly in the joint. "GAMBA combines diverse approaches of osteoarthritis therapy in a unique way", explains GAMBA coordinator Martina Anton from Technical University of Munich. If the researchers succeed, the osteoarthritis therapy of the future could look like this:

Stem cells will be taken from the patient's own bone marrow or fatty tissue. Then the stem cells that are able to turn into bone and cartilage cells over several generations are isolated. At the same time special genes whose code leads to the production of certain proteins are isolated and packaged into gene vectors. These proteins can force the stem cells to turn into cartilage and bone more quickly and thus ensure the urgently needed cell supply in the diseased joint. A further protein is added to prevent possible inflammation in the joint. All these components could ultimately be packaged into special bio-degradable materials and could then be applied directly into the diseased joint, either with a syringe or during surgery. There, the expression of the therapeutic gene can be started from the outside. Only then will the healing proteins – interleukin-10 against inflammation, BMP-2 (bone morphogenetic protein) for bone generation and TGF-ß (transforming growth factor) for the cartilage generation, be generated in the cells.

The starting signal for the gene expression could be given by medication or by special iron oxide particles (commonly used in the clinics), which are also inserted into the joint. "These nanometer sized iron-oxide particles start to vibrate when a magnetic field is applied from the outside. These vibrations lead to the warming of the surrounding tissue", explains GAMBA co-coordinator and nano-expert Christian Plank from Technical University of Munich (1 nanometer = 1 billionth of a meter). A special gene switch that is being placed in front of the genes for the desired proteins reacts to this small rise in temperature and the expression begins.

Eric Farrell from REMEDI Galway calls this localised and time-controlled method the very core of GAMBA: "This possibility to switch the process on and off should prevent any adverse side effects within the body, while at the same time enabling complete control and ensuring an effective induction of the self healing process".

The above-mentioned therapy strategies are currently being tested by the scientists in the project, first in the lab and ultimately in preclinical tests. The ideal outcome would be a three-stage combination which will stop the inflammation as well as causing self healing of bones and cartilage. For every single one of these three processes the best combination of active ingredients needs to be found and then their feasibility has to be proven. However, GAMBA-coordinator Martina Anton warns against excessive hopes: "It's perfectly possible that in the end only one or even none of the three desired healing processes can be achieved by the individual combination of gene therapy, stem cells and bio materials. However, every effort will be made to ensure success!"

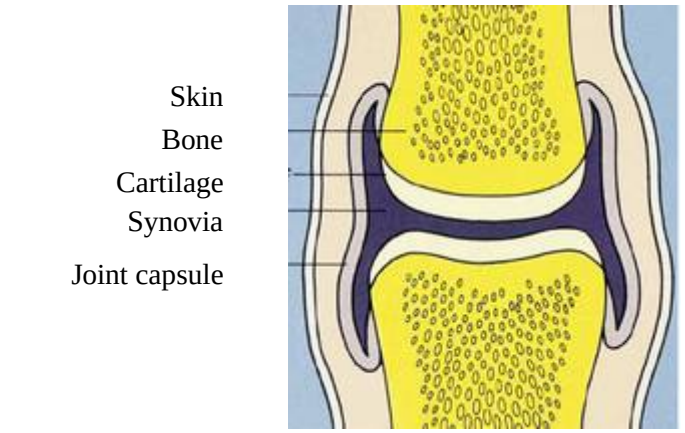
Should one or even several of these GAMBA approaches prove to be effective, further preclinical research will take place after the completion of the project. Finally, there would be clinical studies with patients. The road to a possible market authorisation is a long one. Which means that these new therapies will, in all likelihood, not benefit patients like Bridget M., even if successful.

But she can provide valuable input in discussions focussing on the GAMBA approaches. She can have her say on whether she thinks this research is sensible, realistic or too risky. After all, when stem cell research and new medical gene therapy approaches are combined the chances of a cure are interlinked with new possible risks. Previous gene and stem cell therapies have sometimes resulted in cancer risks. Furthermore, ethical and social aspects need to be discussed.

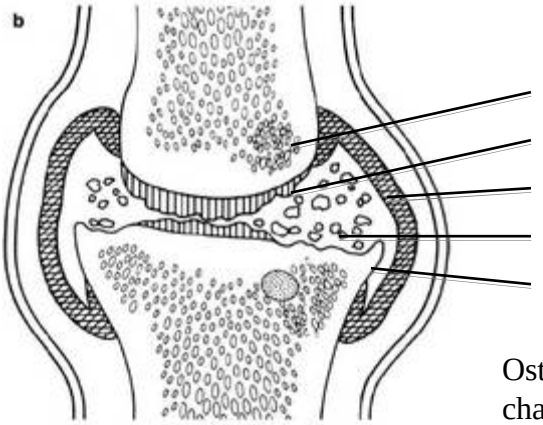
The Irish GAMBA-scientists, Mary Murphy and Eric Farrell, are eagerly waiting to find out which recommendations will emerge from the dialogues with citizens and patients: "The direct feedback from patients and the general population is a novel experience for researchers."

Text: Beatrice Lugger

Healthy Joint



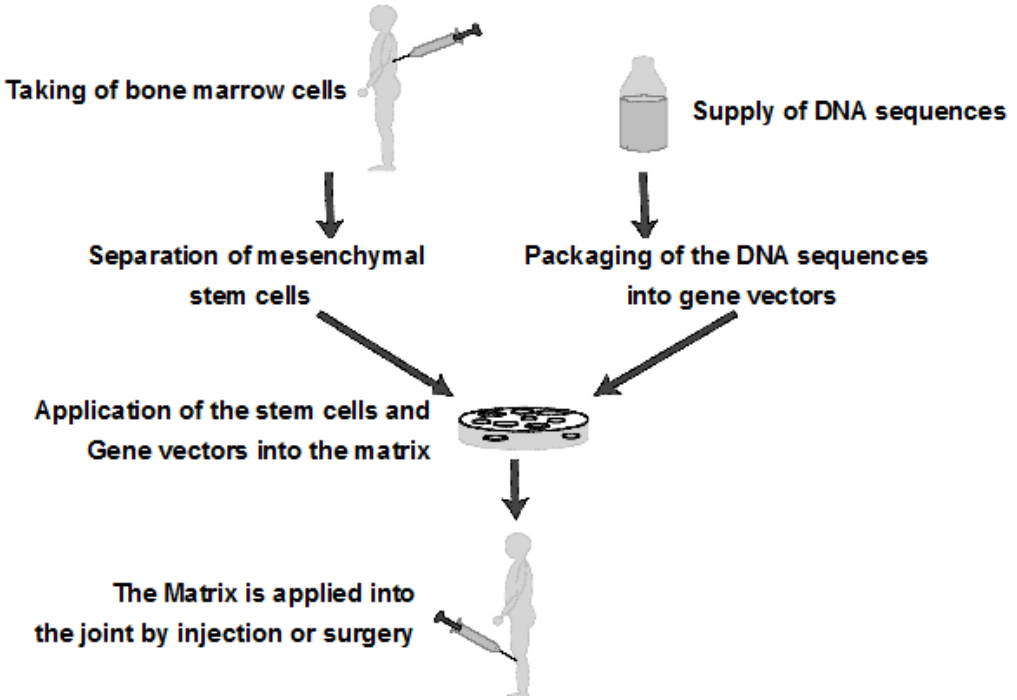
Joint affected by osteoarthritis healing from within



Osteoarthritis always means cartilage defects and changes of the bones

Healing from within

Stem cells from the patient's own body will be taken from the bone marrow. Then the stem cells that are able to turn into bone and cartilage cells over several generations are isolated (mesenchymal stem cells). At the same time DNA sequences, whose code leads to the production of healing proteins are packaged into gene vectors. Stem cells and the gene vectors are then embedded in gels (for the cartilage) or ceramic particles (for the bone). The mix is then applied to the diseased joint with a syringe or during surgery.



Thanks to gene therapy, the cells can also produce healing proteins. These proteins stimulate the stem cells to produce cartilage and bone cells and are effective against inflammation. The joint heals from within.