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Datasheet for the decision of 9 July 2009

Case Number: T 1767/07 - 3.3.08

Application Number: 98922211.2

Publication Number: 0989855

IPC: C12N 5/06

Language of the proceedings: EN

Title of invention:
Osteoarthritis cartilage regeneration using human mesenchymal stem cells

Applicants:
Osiris Therapeutics, Inc., et al

Opponent:
-

Headword:
Osteoarthritis/OSIRIS

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main and first auxiliary requests: inventive step (no)"

Decisions cited:
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Catchword:
-

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Case Number: T 1767/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 9 July 2009

Appellants: Osiris Therapeutics, Inc. et al.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 20 April 2007 refusing European application No. 98922211.2 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
J. Geschwind

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division dated 20 April 2007 to refuse the European patent application No. 98 922 211.2 published under the international publication No. WO 98/51317 with the title "Osteoarthritis cartilage regeneration using human mesenchymal stem cells".

Claims 1, 4, 5, 38, 39 and 40 of the main request refused by the Examining Division read as follows:

"1. Use of cultured human mesenchymal stem cells for the manufacture of a pharmaceutical preparation for regenerating articular cartilage defects in a host in need thereof, wherein said human mesenchymal stem cells having a fibroblastic morphology.

4. Use of claim 1, wherein the pharmaceutical preparation further comprises a chondrogenesis promoting factor.

5. Use of claim 4, wherein the factor is TGF-β3.

38. A composition for the repair of articular cartilage, comprising (i) human mesenchymal stem cells having a fibroblastic morphology, a controlled resorption- biodegradable matrix and IL-1 inhibitors.

39. The composition of claim 18, further comprising a chondrogenesis promoting factor.

40. The composition of claim 19, wherein the molecule is TGF-β3."

II. The examining division came to the conclusion that the main request and auxiliary request I then on file failed to fulfil the novelty and inventive step requirements (Articles 54 and 56 EPC) whereas none of the auxiliary requests II to IV fulfilled the requirement of inventive step (Article 56 EPC).

III. The appellants (applicants) lodged an appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with the same main request and auxiliary requests I to IV as had been refused by the examining division.

IV. The examining division did not rectify its decision and the case was remitted to the board of appeal (cf. Article 109(2) EPC).

V. On 13 February 2009, the board sent a summons to oral proceedings together with a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), making known its preliminary, non-binding opinion as regards the main request, that some of its claims may be lacking novelty or inventive step.

VI. On 9 June 2009, the appellants filed further submissions together with a new main request to replace all the pending claim requests.

Claims 1, 17 and 24 of the new **main request** read as follows:

"1. Use of (i) cultured human mesenchymal stem cells and (ii) TGF-β3 for the manufacture of a pharmaceutical

preparation for regenerating articular cartilage defects in a host in need thereof.

17. A composition for the repair of articular cartilage, comprising (i) human mesenchymal stem cells, (ii) a controlled resorption biodegradable matrix and (iii) TGF-β3."

Claims 2 to 16 related to further features of the use of claim 1. Claims 18 to 23 related to further features of the composition of claim 17. Claims 24 and 25 were directed to the use of TGF-β3 for supporting respectively, mesenchymal stem cells or human bone marrow-derived mesenchymal stem cells to commit to the chondrocyte lineage in culture.

VII. Oral proceedings took place on 9 July 2009. The appellants filed an auxiliary request.

Claim 1 of the **auxiliary request** read as follows:

"1. Use of (i) cultured human **bone marrow-derived** mesenchymal stem cells and (ii) TGF-β3 for the manufacture of a pharmaceutical preparation for regenerating articular cartilage defects in a host in need thereof." (emphasis added by the board)

Claims 2 to 19 were identical to claims 2, 3, 6 to 15, 17, 19 to 21, 23 and 24 of the main request, except that the expression "bone marrow-derived" was added to qualify the mesenchymal cells in claims 14 and 19 (claims 17 and 24 of the main request).

Two documents were introduced into the proceedings, (documents (18) and (19); see infra).

VIII. The documents mentioned in the present decision are the following:

(2): Hunziker, E.B. et al., The Journal of Bone and Joint Surgery, Vol.78.A, No.5, pages 721 to 733, May 1996;

(4): Joyce, M.E. et al., The Journal of Cell Biology, Vol.110, pages 2195 to 2207, June 1990;

(10): US 5 206 023, published on 27 April 1993;

(15): Wakitani, S. et al., The Journal of Bone and Joint Surgery, Vol.76.A, No.4, pages 579 to 592, April 1994;

(18): Barry, F. et al., Experimental Cell Research, Vol.268, pages 189 to 200, 2001;

(19): Kingsley, D.M., Genes and Development, Vol.8, pages 133 to 146, 1994.

IX. The appellants' arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarized as follows:

Main request, claim 1
Article 56 EPC, inventive step

The closest prior art was document (15) which related to the repair of defects in the articular cartilage of

rabbits. A population of bone marrow osteochondral progenitor cells was transplanted into the damaged area of the cartilage and a study was carried out of the tissues formed at that site from two to twenty-four weeks after transplantation. No transforming growth factors were added to the cell population.

Starting from the closest prior art, the problem to be solved could be defined as providing improved means for treating human cartilage defects.

The solution provided was a pharmaceutical composition comprising human mesenchymal stem cells together with the transforming growth factor TGF-β3.

The inventors were able to show that TGF-β3 increased the rate of formation of cartilage cells (chondrocytes) in vivo in an implant and also that it helped mesenchymal stem cells in culture to commit quickly to the chondrocyte lineage. Page 19 of the application provided the relevant disclosure in this respect, teaching the skilled person that TGF-β3 was more efficient than TGF-β1 and caused suppression of Type I collagen. Example I showed that in the presence of TGF-β3, bone marrow-derived mesenchymal stem cells cultured in vitro produced more extracellular matrix than in its absence, the differentiation process resulting in the formation of hypertrophic cells. These results were fully unexpected as neither document (15) nor any other documents of the prior art suggested the use of TGF-β3 and its advantages.

In document (10), a totally different approach was taken to cartilage repair. It was taught to administer

a proliferating agent (TGF-β), a transforming agent and a matrix at the damage site of the cartilage **in the absence of any cells**, on the assumption that some undefined cells - simply identified as repair cells - would migrate from where they happened to be in vivo to the damaged area where their proliferation would be stimulated by the combination of the agents and the matrix. Thus, document (10) did not provide any evidence that TGF-β3 was able to help the differentiation of mesenchymal stem cells into chondrocytes. In particular, the passage in column 9, lines 6 to 16 referring to a number of transforming growth factors was purely speculative. In any case, some years later, the inventor designated in document (10) published a scientific article, document (2) on file, which showed that by using this approach, it was not in fact possible to achieve differentiation of the undefined repair cells into chondrocytes even in the presence of TGF-β1 or TGF-β2. Faced with these teachings, the skilled person would doubt that members of the TGF-β family, whichever they might be, would help in the differentiation of mesenchymal stem cells into chondrocytes.

The skilled person would also doubt that the teachings of document (4) as regards the use of TGF-β1 for initiating chondrogenesis of undifferentiated mesenchymal cells at the site of a cartilage defect could be transferred with a reasonable expectation of success of TGF-β3. Indeed, TGF-β1 and TGF-β3 only presented limited sequence homology (70%). They were known to be coupled to different responding molecules in different tissues and, thus, would not be expected "to act alike". Furthermore, members of the TGF-β

family were shown in document (4) to promote Type I collagen formation, which collagen mostly was a constituent of bones. This was undesirable when aiming at the repair of cartilage defects. The present inventors were the first to show that TGF-β3 was particularly and unexpectedly advantageous since it suppressed type I collagen formation. Document (18) to be taken as an expert document, confirmed firstly that TGF-β isoforms differed in their effects on chondroprogenitor cells and, secondly, that TGF-β3 was more effective than TGF-β1 in promoting chondrogenesis.

In favour of inventive step, the following observations must also be taken into consideration:

- The skilled person aware of the teachings in document (4) that TGF-β1 or TGF-β2 might be useful in accelerating chondrogenesis and desirous to solve the above mentioned problem would try and vary the experimental conditions in which either one of them should be used in order to get a better effect. He/she would have no reasons to turn specifically to TGF-β3 as the transforming growth factor family was extremely large (cf. document (19)). Singling out TGF-β3 could only be done with the hindsight knowledge of the invention.

- One could not extrapolate from the in vivo experimental settings described in the cited documents to an in vitro situation. Even if the skilled person took into consideration the combined teaching of documents (15) and (4), he/she had no reasonable expectation of success when attempting to arrive at the claimed invention. Indeed, while human mesenchymal stem

cells were used in document (15), this was **in the absence of transforming growth factor** whereas the chondrogenesis disclosed in document (4) as taking place in the presence of TGF-β1 or TGF-β2 was **not that of human stem cells**. It could not even be regarded as the chondrogenesis of stem cells since the cells were simply defined as undifferentiated mesenchymal cells from the periosteum.

For all these reasons, inventive step must be acknowledged.

Auxiliary request; claim 1
Article 56 EPC; inventive step

Claim 1 of this request was limited to the use of **bone marrow-derived** stem cells and TGF-β3 for the preparation of a pharmaceutical composition. This limitation took the claimed subject-matter even further away from the teachings in the prior art documents (15), (10), (2) or (4). It was fully surprising that bone marrow cells could be differentiated into chondrocytes in vitro in the presence of TGF-β3, when bone marrow was a tissue quite different from bone or cartilage tissues. It also had to be kept in mind that the cells which were said in document (10) to undergo differentiation, were not **bone marrow** stem cells but originated from the **synovial membrane** (document (2)) and that the cells used in document (4) to study differentiation in the presence of TGF-β1 or TGF-β2 were undifferentiated cells from the **periosteum**. Not all mesenchymal or undifferentiated cells shared the same properties irrespective of their origin. For these

reasons, the teachings of the cited prior art documents did not render the claimed subject-matter obvious.

X. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 25 of the request filed on 9 June 2009 or on the basis of the auxiliary request filed during the oral proceedings.

Reasons for the decision

Oral proceedings

1. Two new documents were presented by the appellants which were considered by the board to be prima facie relevant. They were introduced into the proceedings pursuant to Article 114(1) EPC (documents (18) and (19), supra, section VIII).

2. It was remarked by the board that some of the dependent claims of the main request may not comply with the requirements of Article 123(2) EPC. However, inventive step being the key issue, its assessment forms the basis of the present decision.

Main request; claim 1
Article 56 EPC; inventive step

3. The closest prior art is document (15) which relates to "Mesenchymal Cell-Based Repair of Large, Full-Thickness Defects of Articular Cartilage." Osteochondral progenitor cells referred to by the authors as mesenchymal stem cells, are isolated from rabbits' bone

marrow, grown in culture, dispersed in Type I collagen - used as a delivery vehicle - and transplanted into defects in the rabbits medial femora condyle (passage bridging the left- and right- hand columns on page 580). A study is then carried out of the repair tissues formed in situ from the second to the twenty-fourth week after transplantation. It is mentioned on page 580, left-hand column, that the bone marrow mesenchymal stem cells "proliferate (grow) in culture without loss of the ability to form bone or cartilage" and on page 588, right-hand column, that the events which occurred after transplantation "resulted in the formation of articular cartilage on subchondral bone, which, in effect, resulted in the resurfacing of the condyle". In the discussion part of the article (page 589), a hypothetical sequence of these events is proposed, the first one being that the implanted collagenous delivery vehicle is infused with bioactive agents provided both from the site of the wound itself and systemically. It is stated in the left-hand column, third full paragraph:

"There are several important aspects of our hypotheses for which substantial support is already available in the literature. Injured bone rapidly disburses and attracts potent biofactors, the most often studied of which are the **transforming growth-factor-beta family** or the bone morphogenetic proteins. **These factors function to convert osteochondral progenitor cells into chondrocytes**... It must be stressed that the target of these bioactive factors is **mesenchymal stem cells**..." (emphasis added by the board) and, finally, on page 590, end of the text:

"The procedures have considerable relevance to the treatment of defects in the cartilage of humans and provide the basis for the development of a repair technology that is capable of regenerating large areas of articular cartilage."

4. Starting from the closest prior art, the problem to be solved may be defined as the provision of improved means for repairing defects in human cartilage.

5. Formulating this problem does not in itself require inventive step if only because the last paragraph in document (15) suggests that the results achieved until then should be regarded as a basis for further development. It is moreover clear that the rabbit model is used in the perspective of a clinical use in humans.

6. The proposed solution is a pharmaceutical composition comprising human mesenchymal stem cells and the transforming growth factor, TGF-β3.

7. The correlation made in document (15) between the unidentified in vivo bioactive agents allowing rapid conversion of the bone marrow-derived mesenchymal stem cells into chondrocytes and the members of the TGF-β family is undoubtedly a suggestion, albeit indirect, that members of the TGF-β family may be important for the formation of cartilage and bone starting from mesenchymal stem cells. The same observation is made in document (4), "Transforming Growth Factor-β and the Initiation of Chondrogenesis and Osteogenesis in the Rat Femur" which, furthermore, provides a straightforward teaching in this respect. Daily injections of TGF-β1 or TGF-β2 in the subperiosteal

region of newborn rat femur is shown to result in localized intramembranous bone formation and chondrogenesis. On page 2197, it is disclosed:

"The periosteum is comprised of two tissue layers: an outer fibroblast layer and an inner region of **undifferentiated mesenchymal cells** (14,30). Extensive studies of fracture healing have demonstrated that this **mesenchymal cell population is the likely source of chondrocyte and osteoblast precursor cells** (51)." (emphasis added by the board)

It is observed on page 2203, right-hand column, that:

"Our results suggest that not only can TGF-β induce the differentiation of periosteal mesenchymal cells into osteoblasts and chondrocytes but it can also stimulate these cells to proliferate and synthesize the extracellular matrix proteins characteristic of bone and cartilage."

On page 2204, it is mentioned that TGF-β2 is more efficient at inducing the formation of bone and cartilage than TGF-β1 although the relative ratio bone to cartilage is not significantly different.

8. In the board's judgement, the skilled person faced with the combined teachings that, on the one hand, mesenchymal stem cells may be cultured in vitro without loosing their capacity for differentiation (document (15)) and that, on the other, the transforming growth factors TGF-β1 or TGF-β2 have a definite impact on the proliferation of primitive mesenchymal cells would find it obvious to manufacture a pharmaceutical composition

comprising at the same time mesenchymal stem cells and a **TGF-β** in order to solve the above mentioned problem.

9. The present invention is, however, specific in that it is **TGF-β3** which is included in the pharmaceutical preparation. The questions to be answered are, thus, whether or not using TGF-β3 could be regarded as a purposive unexpected choice and whether or not some unexpected advantage is linked to its use.

10. In this respect, the appellants argued that, aware of the properties of TGF-β1 or TGF-β2, the skilled person desirous to solve the above mentioned problem would choose to optimize the experimental conditions in which these factors are used. This is certainly one alternative which is directly derivable from the results obtained in document (4) that the relative amounts of bone and cartilage formed is dose dependent on the amount of TGF-β (eg. passage bridging pages 2201 and 2202). In the board's judgement, it is equally obvious in view of the teachings in document (15) that members of the TGF-β family **in general** function to convert osteochondral progenitor cells into chondrocytes, to test the members of the family other than TGF-β1 and TGF-β2. It is understood that there are three further members in the TGF-β family, which is defined in document (19) as a distinct subfamily of the TGF-β superfamily (see page 134; "New members and families within families"). This number is not so high that an attempt at investigating the properties of the TGF-β members other than TGF-βI or TGF-β2 should be regarded as anything else than a matter of **try and see**. Accordingly, it cannot be said that the choice of TGF-β3 is a purposive choice which is only obvious with the

hindsight knowledge of the invention. In the board's judgment, there was no need for a choice to be made.

11. A last point in this respect is that, contrary to the appellants' opinion, the board finds itself unable to see the 70% homology between TGF-β1 and TGF-β3 as a deterrent from testing TGF-β3. Indeed, this is the same percentage of homology as exists between TGF-β1 and TGF-β2 (document (4), page 2205), both factors being able to accelerate chondrogenesis. If taken into account at all, this percentage of homology would encourage the skilled person to test TGF-β3.

12. Of course, it could be that TGF-β3 would have such unexpected properties as would warrant acknowledgment of inventive step. In this context, the appellants point out to the passage on page 19 of the application as filed which teaches that TGF-β3 causes suppression of type I collagen as showing a definite advantage of using TGF-β3, since the ultimate aim of the invention is to facilitate the formation of cartilage, if need be at the expense of the formation of bone which requires Type I collagen. However, this scant reference to TGF-β3 causing suppression of type I collagen is not made plausible by any data in the application per se. When asked by the board for further evidence to this point, the appellants put forward document (18) - published in 2001, to be regarded as an expert opinion - and drew the board's attention to the passage on page 195:

" Three isoforms of TGF-β have the ability to induce this response, and under the conditions of culture described here the initial appearance of mRNA coding for cartilage matrix components becomes evident within

24h. Both TGF-β2 and TGF-β3 are more effective than TGF-β1 in promoting chondrogenesis ..."

However, no passages were pointed out which would teach the skilled person the suppressive effect of TGF-β3 on Type I collagen production. Furthermore, one derives from the above cited passage that there is no significant differences between the properties of TGF-β2 and TGF-β3. Neither the application as filed nor the post-published evidence highlight a specific property of TGF-β3 which would warrant acknowledgement of inventive step.

13. The contents of documents (10) and (2) were also discussed. Document (10) proposes a method for repairing defects in the cartilage of humans or animals whereby growth factors - amongst them TGF-β1 or TGF-β2 - are injected into the damaged area as proliferation and chemotactic agents. Unidentified cells present in the subject to be treated (repair cells) are expected to migrate to this site and differentiate into chondrocytes under their stimuli. Positive results in terms of tissue formation were apparently observed as hyaline cartilage tissue was produced (Examples 5 to 7). However, according to the appellants, this teaching is to be evaluated in the light of document (2) - published some years later and having as an author the inventor designated in document (10) - which reproduces equivalent experiments, identifies the repair cells as mesenchymal stem cells of synovial origin and comes to the conclusion on page 731, that:

"Cartilage did not form in any of the experiments in which a growth factor was included in the fibrin matrix."

In their view, these data would discourage the skilled person from pursuing the aim of repairing cartilage defects by using a TGF-β. Of course, negative results would discourage the skilled person to reproduce an approach which led to these results. However, as was pointed out by the appellant himself (section IX, supra), the approach in document (10) or (2) is quite different from the approach taken in the closest prior art and in the present application. Thus, it cannot be expected to have any negative implications on this latter approach.

14. Finally, the technical differences between the teachings of the prior art and those of the present application were argued to deprive the skilled person from a reasonable expectation of success when conceiving the present invention. Hence, it was observed that document (15) did not teach the use of a TGF-β, whereas document (4) was not concerned with human mesenchymal stem cells, not even with the differentiation of rat mesenchymal stem cells but only with the differentiation of rat undifferentiated mesenchymal cells. Here, the board wants to remark as follows: the existence of technical differences is generally enough to establish novelty. Yet, it is generally not sufficient to establish inventive step on the basis of "a lack of reasonable expectation of success". In this last framework, a causality link must be established between the differences observed and the likely existence of technical hindrances susceptible to

affect the end result, the solution of which would justify acknowledgement of inventive step. No such causality link was established here. The argument is, thus, not relevant.

15. For these reasons, the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary request; claim 1
Article 56 EPC; inventive step

16. Claim 1 of this request differs from claim 1 of the main request in that it is human **bone marrow-derived** mesenchymal stem cells which are intended to be used for the manufacture of the pharmaceutical composition. The reasons why this added feature would impart inventive step to the claimed subject-matter were not explained any further than by saying it was one more difference with the prior art and that mesenchymal stem cells of different origins would be expected to behave differently.

17. Contrary to the appellants, the board finds that the use of mesenchymal stem cells of the same origin as now claimed, ie. bone marrow, was already disclosed in the prior art. In fact, it is mentioned on page 588 of the closest prior art document (15):

"Previous reports from our laboratory have noted that **bone-marrow** or periosteum-derived cells, which we have called **mesenchymal stem cells**, have both osteogenic and chondral potential when tested in either ***in vivo*** or ***in vitro*** systems...These mesenchymal-stem-cell preparations rapidly differentiated into chondrocytes

in defects of the distal femoral condyle of the rabbit." (emphasis added by the board)

18. The reasoning developed supra in relation to claim 1 of the main request - particularly in point 14 as regards the value of a difference in the assessment of inventive step - equally applies here.

19. For these reasons, the auxiliary request is rejected for failing to fulfil the requirement of Article 56 EPC.

Order:

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar The Chairman

A. Wolinski L. Galigani