There is currently no cure for type II collagenopathies, and current care consists in managing and treating symptoms, including invasive surgeries (11).

To better understand the mechanisms of said pathologies, some authors tried to develop animal or cellular models. Okada et al. have generated new cellular models by converting patient fibroblasts from patients with achondrogenesis into induced chondrocytic cells or by generating iPS cells (12). In this study, they attempted to decrease endoplasmic reticulum (ER) stress or to enhance other cartilage signaling pathways such as BMP signaling, showing some potential benefit, but most importantly they developed a cellular model that will be useful for pathophysiological studies and drug screening.

Anyway, there still exists a serious and unfulfilled need for a curative treatment of type II collagenopathies.

SUMMARY

The inventors have surprisingly developed a gene therapy approach to restore bone growth, particularly in SEDC. The aim is to provide the altered growth plate cartilage with normal collagen type II, thus allowing for a reorganization of the cartilage matrix which permits bone growth. Specifically, this gene therapy approach is allowed thanks to designed hybrid promoters, which are able to significantly express type II collagen in bone cells, while being specific in that they limit expression to tissues naturally expressing type II collagen.

Thus, in a one aspect, the present disclosure refers to a promoter comprising the nucleic acid sequence SEQ ID NO:1, in which a fragment starting from position A and ending at position B of said sequence SEQ ID NO:1 has been substituted by a fragment of the hEF1α promoter comprising at least the TATA box, wherein position A is comprised between nucleotides 521 and 555 of SEQ ID NO:1, and position B is comprised between nucleotides 560 and 587 of SEQ ID NO:1, andwherein the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 may be present or absent, wherein the fragment of the hEF1α promoter comprising at least the TATA box is chosen from sequences SEQ ID NO:2, 3 and 4. In one example, there is disclosed a promoter comprising the nucleic acid sequence SEQ ID NO:1, in which a fragment starting from position A and ending at position B of said sequence SEQ ID NO:1 has been substituted by a fragment of the hEF1α promoter comprising at least the TATA box,

wherein position A is comprised between nucleotides 521 and 555 of SEQ ID NO:1, and position B is comprised between nucleotides 560 and 587 of SEQ ID NO:1, and

wherein the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 may be present or absent.

Such a promoter is a hybrid promoter, and is a promoter according to the invention.

In a second aspect, the disclosure refers to a vector comprising the promoter as disclosed herein.

In a third aspect, the present disclosure refers to the use of the promoter or of the vector as disclosed herein, in therapy. In another aspect, the present disclosure refers to a promotor or vector as disclosed herein for use in gene therapy. Particularly, said use is for gene therapy, such as an *ex vivo* gene therapy or an *in vivo* gene therapy.

In a fourth aspect, the present disclosure refers to the use of the promoter or of the vector disclosed herein in the manufacture of a medicament for for treating a skeletal dysplasia or a disease of the musculoskeletal system.

In a fifth aspect, the to the present disclosure refers to the use of the promoter or of the vector as disclosed herein for use in the manufacture of a medicament for treating a type II collagenopathy.

DETAILED DESCRIPTION OF THE INVENTION

As shown in the example, the inventors have surprisingly developed a gene therapy to restore bone growth, particularly in the case of type II collagenopathies such as SEDC. Such an approach is very surprising, because the complex synthesis of type II collagen must be performed at the site of the disease (i.e. in the chondrocytes). On the other hand, it is known that the viruses have a very limited penetration into the hyaline cartilage matrix.

Surprisingly, the inventors have been successful in preparing a specific hybrid promoter which was integrated into a vector in which it controls the expression of the pro-alpha1(II) chain of type II collagen (encoded by COL2A1 gene), and said vector is able to penetrate into the growth plate. This was not expected: hyaline cartilage and growth cartilage are two separate and different structures, and the vector which comprises the hybrid promoter is able to penetrate into the growth plate, whereas it is not able to penetrate the hyaline cartilage.

Moreover, once injected into cells, said vector induces the specific expression of type II collagen by chondrocytes as compared to other cells such as B lymphocytes; it is thus tissue specific (as shown in Figure 7). Furthermore, said expression is high in chondrocytes.

After *in vivo* injection of said vector into a murine model of type II collagenopathy, a significant increase of survival is observed. This increased survival is associated with a restoration of the rib cage volume and of the foramen magnum area, and with a correction of the position of the skull following treatment. Moreover, body and long bones growth

CLAIMS

1. Promoter comprising the nucleic acid sequence SEQ ID NO:1, in which a fragment starting from position A and ending at position B of said sequence SEQ ID NO:1 has been substituted by a fragment of the hEF1α promoter comprising at least the TATA box,
wherein position A is comprised between nucleotides 521 and 555 of SEQ ID NO:1, and position B is comprised between nucleotides 560 and 587 of SEQ ID NO:1, and
wherein the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 may be present or absent, wherein the fragment of the hEF1α promoter comprising at least the TATA box is chosen from sequences SEQ ID NO:2, 3 and 4.

2. Promoter according to claim 1, wherein the fragment starting from nucleotide 541 and ending at nucleotide 560 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:2, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is absent.

3. Promoter according to claim 1, wherein the fragment starting from nucleotide 541 and ending at nucleotide 560 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:2, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is present.

4. Promoter according to claim 1, wherein the fragment starting from nucleotide 555 and ending at nucleotide 560 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:3, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is absent.

5. Promoter according to claim 1, wherein the fragment starting from nucleotide 555 and ending at nucleotide 560 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:3, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is present.

6. Promoter according to claim 1, wherein the fragment starting from nucleotide 521 and ending at nucleotide 587 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:4, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is absent.

7. Promoter according to claim 1, wherein the fragment starting from nucleotide 521 and ending at nucleotide 587 of sequence SEQ ID NO:1 has been substituted by the fragment of the hEF1α promoter comprising at least the TATA box of sequence SEQ ID NO:4, and
the fragment consisting of nucleotides 598 to 607 of SEQ ID NO:1 is present.

8. Vector comprising the promoter according to any one of claims 1 to 7.

9. Vector according to claim 8, in which the promoter controls the expression of a gene or a fragment thereof coding for a collagen chain, preferably COL2A1.

10. Promoter according to any one of claims 1 to 7, or vector according to claim 8 or 9, for use in therapy.

11. Promoter according to any one of claims 1 to 7, or vector according to claim 8 or 9, for use in gene therapy.

12. Use of the promoter according to any one of claims 1 to 7, or the vector according to claim 8 or 9, in the manufacture of a medicament for treating a skeletal dysplasia or a disease of the musculoskeletal system.

13. Use of the promoter according to any one of claims 1 to 7 or 12, or the vector according to claim 8 or 9 or 12, in the manufacture of a medicament for treating a type II collagenopathy.

14. The use according to claim 13, wherein the type II collagenopathy is spondyloepiphyseal dysplasia congenital (SEDC).