

oncogenes and cellular receptors for animal viruses. Most early approaches were based on the use of pooled libraries (typically, cDNA libraries), in which a desired factor was identified by phenotype-based selection. In the 2000s, along with advancements in robotics, library screening progressively moved toward high throughput screening (HTS) analysis, based on the use of arrayed libraries. HTS has paved the way to the use not only of cDNA libraries, but also of libraries of peptides, nucleic acids (Eulalio, A., et al. Functional screening identifies miRNAs inducing cardiac regeneration. *Nature* 492, 376-381 (2012)) and small molecules. Today, the advances in gene transfer permit the field to take a further step forward, namely to screen libraries directly in animals, thus moving from biochemical or phenotypic selection in vitro towards true functional selection in vivo.

SUMMARY

[12] The inventors have utilized a unique procedure based on the in vivo Functional Selection (FunSel) of factors exerting a desired function to identify factors with cardioprotective effects. The inventors' procedure is based on the use of a library of AAV vectors, which are exquisite tools for highly efficient cardiac gene transfer.

[13] Of note, factor identification by FunSel does not require that the selected factors play a role in a given tissue during normal physiology, thus extending the range of potentially therapeutic proteins to all secreted factors encoded by the genome.

[14] The inventors have surprisingly found that the three factors Chrdl1 (Chordin-like protein 1), Fam3c and Fam3b, although exerting completely different biological activities, commonly share cardioprotective effects.

[15] The three novel cardioprotective proteins Chrdl1, Fam3c and Fam3b are highly homologous between mouse and humans (93%, 94% and 79% respectively).

[16] These three factors protect from cardiac cell death induced by ischemia and other kind of damage, including treatment with chemotherapeutic agents.

[17] Accordingly, the present disclosure relates to the factors Chrdl1, Fam3c and Fam3b for use as medicaments.

[18] In one example, the disclosure provides a protein selected from the group consisting of Chrdl1, Fam3c, Fam3b and fragments thereof, or a polynucleotide encoding therefor, for use in treating or reducing the risk of heart disease. In one aspect, the present disclosure refers to the use of Fam3c or a fragment thereof, or a polynucleotide encoding therefor, in the manufacture of a medicament for treating or reducing the risk of

heart disease, wherein the Fam3c or fragment thereof comprises an amino acid sequence that has at least 80% identity to SEQ ID NO: 2. In another aspect, the present disclosure refers to the use of a vector in the manufacture of a medicament for treating or reducing the risk of heart disease, wherein the vector comprises a polynucleotide as disclosed herein. In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the Fam3c or fragment thereof as disclosed herein and a pharmaceutically acceptable vehicle and/or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the vector as disclosed herein and a pharmaceutically acceptable vehicle and/or excipient. In another aspect, the present disclosure refers to the use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating or reducing the risk of heart disease.

CLAIMS

1. Use of Fam3c or a fragment thereof, or a polynucleotide encoding therefor, in the manufacture of a medicament for treating or reducing the risk of heart disease, wherein the Fam3c or fragment thereof comprises an amino acid sequence that has at least 80% identity to SEQ ID NO: 2.
2. The use of claim 1, wherein the Fam3c or fragment thereof, or polynucleotide encoding therefor, preserves cardiac muscle cell viability.
3. The use according to claim 1 or 2, wherein the Fam3c fragment comprises the amino acid sequence of SEQ ID NO: 2 not bearing the signal peptide or is a fragment secreted into the extracellular environment of a cell.
4. The use according to claim 1 or 2, wherein the polynucleotide comprises a nucleotide sequence that has at least 70% identity to SEQ ID NO: 5.
5. The use according to any preceding claim, wherein the heart disease is associated with cardiac ischemia or loss of cardiomyocytes.
6. The use according to any preceding claim, wherein the heart disease is selected from myocardial infarction; loss of cardiomyocytes as a consequence of myocardial infarction; reperfusion-injury after percutaneous coronary intervention; myocarditis; hypertension; cardiac toxic damage (in particular, by chemotherapy); or cardiomyopathy.
7. The use according to any preceding claim, wherein the heart is protected from myocardial infarction; cardiac function is preserved after myocardial infarction or percutaneous coronary intervention; or fibrosis after infarction is reduced.
8. The use according to any preceding claim, wherein heart failure is prevented.
9. The use according to any preceding claim, wherein the Fam3c or fragment thereof is glycosylated.
10. The use according to any preceding claim, wherein the Fam3c or fragment thereof is a fusion protein, preferably an Fc fusion protein.
11. Use of a vector in the manufacture of a medicament for treating or reducing the risk of heart disease, wherein the vector comprises a polynucleotide as defined in any one of claims 1-8.

12. The use according to claim 11, wherein the vector is a viral vector, optionally wherein the viral vector is an adeno-associated viral (AAV) vector.
13. A pharmaceutical composition comprising the Fam3c or fragment thereof as defined in any one of claims 1-10 and a pharmaceutically acceptable vehicle and/or excipient.
14. The pharmaceutical composition according to claim 13, wherein the composition is formulated for injection.
15. A pharmaceutical composition comprising the vector as defined in claim 11 or 12 and a pharmaceutically acceptable vehicle and/or excipient.
16. Use of the pharmaceutical composition according to any one of claims 13-15 in the manufacture of a medicament for treating or reducing the risk of heart disease.
17. The use of claim 16, wherein the pharmaceutical composition preserves cardiac muscle cell viability.