CLAIMS

1. An *in vitro*-differentiated human cardiomyocyte comprising reduced expression of HCN4, CACNA1H, and SLC8A1 and expression of a transgene encoding KCNJ2 that is controlled by an endogenous HCN4 regulatory sequence.

2. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which HCN4, CACNA1H, and SLC8A1 activities are partially or completely inhibited by genetic manipulation, and KCNJ2 activity is at least partially stimulated, as compared to a control cell.

3. An *in vitro*-differentiated human cardiomyocyte according to Claim 2, in which HCN4, CACNA1H, and SLC8A1 activities are inhibited by genetic manipulation by at least 10% or 1-fold, and KCNJ2 activity is stimulated by at least 10% or 1-fold, as compared to a control cell that has not been manipulated by genetic manipulation.

4. An *in vitro*-differentiated human cardiomyocyte according to Claim 2, in which the genetic manipulation method is gene knock out or gene inactivation, and optionally in which the gene knock out is by way of inducing an insertion or a deletion in the gene using a gene editing system, in which the gene editing system is optionally selected from the group consisting of ZFNs, TALENs, meganucleases, transposases, CRISPR/Cas systems, nickase systems, base editing systems, prime editing systems, and gene writing systems.

5. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which the gene knock out of HCN4, CACNA1H, or SLC8A1 results in reduced protein expression and/or reduced gene expression of HCN4, CACNA1H, or SLC8A1, or in which the gene inactivation comprises insertion or deletion of nucleic acid sequence at the locus encoding HCN4, CACNA1H and/or SLC8A1.

6. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which a KCNJ2 coding sequence replaces a coding sequence of HCN4 or CACNA1H, such that the replaced HCN4 or CACNA1H coding sequence is not expressed and the replaced KCNJ2 is expressed under the control of an endogenous HCN4 or CACNA1H regulatory sequence

7. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which the genes encoding HCN4, CACNA1H and SLC8A1 are inactivated, and the KCNJ2 polypeptide is overexpressed.

8. An *in vitro*-differentiated human cardiomyocyte according to Claim 7, in which the genes encoding HCN4, CACNA1H, and SCL8A1 comprise an indel in at least one allele.

9. An *in vitro*-differentiated human cardiomyocyte according to Claim 8, in which the *in vitro*-differentiated human cardiomyocyte is a $HCN4^{indel/indel}$, $CACNA1H^{indel/indel}$, and $SCL8A1^{indel/indel}$ cell.

10. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which the genes encoding HCN4, CACNA1H and SLC8A1 are inactivated using a CRISPR/Cas system, and the KCNJ2 polypeptide is overexpressed under the control of an endogenous HCN4 regulatory sequence or under the control of an endogenous CACNA1H regulatory sequence.

11. An *in vitro*-differentiated human cardiomyocyte according to Claim 1, in which the cardiomyocyte is *in vitro* differentiated from a pluripotent stem cell or from a starting material.

12. An *in vitro*-differentiated human cardiomyocyte according to Claim 11, in which the cardiomyocyte is *in vitro*-differentiated from a starting material, or an iPSC derived from a subject to whom the *in vitro*-differentiated human cardiomyocyte is to be transplanted or from a healthy subject.

13. An *in vitro*-differentiated human cardiomyocyte according to Claim 12, in which the starting material is selected from any of:

primary cells collected from a donor, optionally in which the primary cells are stem cells;

a stem cell line; or

iPSC.

14. Use of an *in vitro*-differentiated human cardiomyocyte according to Claim 1 in the manufacture of a medicament for reducing arrhythmia in a subject, in which the medicament comprising the *in vitro*-differentiated human cardiomyocytes is to be administered to cardiac tissue of a subject in need thereof, in which the *in vitro*-differentiated human cardiomyocytes upon administration promote reduced arrhythmia relative to a subject administered *in vitro*-differentiated human cardiomyocytes that do not comprise at least partial inhibition of HCN4, CACNA1H and SLC8A1 activities and at least partial stimulation of KCNJ2 activity.

15. Use according to Claim 14, in which upon administration to cardiac tissue of a subject in need thereof, the subject experiences reduced arrhythmia relative to a subject administered *in vitro*-differentiated human cardiomyocytes that do not comprise at least partial inhibition of HCN4, CACNA1H and SLC8A1 activities and at least partial stimulation of KCNJ2 activity.

16. A pluripotent stem cell comprising reduced protein expression and/or reduced gene expression of HCN4, CACNA1H and SLC8A1, and increased protein expression and/or increased gene expression of KCNJ2.

17. A cardiomyocyte differentiated *in vitro* from the pluripotent stem cell according to Claim 16.

18. A pharmaceutical composition comprising an *in vitro*-differentiated human cardiomyocyte of or derived from any preceding claim, and a pharmaceutically-acceptable carrier.

19. Use of *in vitro* differentiated cardiomyocyte of, or derived from any of Claims 1 to 17 for preparation of a medicament for the treatment of a disease or disorder involving cardiac tissue damage or dysfunction in a subject in need thereof, in which the medicament comprising the *in vitro* differentiated cardiomyocyte of or derived from any of Claims 1 to 17 or a pharmaceutical composition according to Claim 18 are to be delivered to cardiac tissue of a subject in need thereof.

20. Use according to Claim 19, in which the contacting or delivering results in reduced engraftment arrhythmia relative to transplant of *in vitro*-differentiated cardiomyocytes lacking the inhibition of HCN4, CACNA1H and SLC8A1 and lacking the stimulation of KCNJ2.