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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Fibrosis in murine hearts was assessed in Masson Trichrome stained heart sections that were imaged at 20x, 10x and 4x magnification using Image-Pro 7.0. Electrocardiography in mice was carried out using Vivid 7 Dimension ultrasound system (GE Healthcare Ultrasound, Horten, Norway). Assessment of AF inducibility was performed by iox2 software (version 2.8.0.13, EMKA technologies, FR). Surface ECG & catheter signals were recorded and analysed using IOX2 software (version 2.8.0.13 and 2.9.5.28, EMKA technologies, FR). Cell sorting was carried out on a Becton Dickinson (BD) FACS Aria Fusion III sorter using a 100 µm nozzle and FACSDiva software v8. Cleaned peptides were separated on a nanoflow LC system (Thermo Scientific Dionex UltiMate 3000 RSLCnano); Fluorescence signal in BMP1 activity assay was measured by the fluorescence plate reader (Molecular Devices SpectraMax M2) at the excitation and emission wavelengths of 320 nm and 405 nm respectively. Scar-in-a-jar data were collected using operetta High Content Imaging System v4.9 (PerkinElmer). Imaging of primary cells and cell lines was performed with a Zeiss LSM 710 or Leica DM 6000 CFS confocal imaging system. To assess cellular localisation of the CTR, optical sections of fibroblasts were imaged with a frame size of 157 µm x 157 µm at a z-depth of 1 µm and pixel resolution of 0.09 µm x 0.09 µm. Channels were subsequently split and then merged in Fiji open source software (version 2.0.0-rc-69/1.52i).
Data analysis	bcl2fastq version 2.20.0.422 - Fastq file conversion from raw bcl format FastQC Version 0.11.8 Software (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/) - Raw sequence data quality control software. STAR Version 2.4.2 - Transcriptome alignment. Cutadapt Version 1.16 - Sequence data trimming Picard Subread Version 1.6.2 - feature count summary Cellranger pipeline version 3.1.0 - 10x raw data processing. R Version 3.5.3 and 3.4.2 - Language for statistical analysis. limma 3.34.5 The following packages were used in addition to base installation: Seurat Bioconductor R Package, Version 3.1.5.9900 - single cell data QC, normalisation, clustering and differential gene expression analysis.

irlba, R Package, Version 2.3.2 - Principal component analysis.
clusterProfiler, Bioconductor R Package, Version 3.6.0 - Gene Ontology enrichment analysis.
ggplot2, R Package, Version 2.2.1 - Plotting package.
DESeq2, Bioconductor R Package, Version 1.20.0 - Differential expression analysis of bulk /pseudobulk RNA sequencing data.
uwot R package Version 0.1.8 - UMAP visualisations
MAST R package, Version 1.8.2 - Single Cell differential gene expression
DropletUtils R package, Version 1.2.2 - data cleaning and cell identification
sctransform R package, version 0.2.1 - data normalisation
FLUOstar Omega software version 5.11, firmware version 1.43 (BMG LABTECH, Germany)
Affymetrix Genechip Command Console software (1.4.1.46)
SoftMax ProSoftware v5.0
ImageJ software (version 1.52a)
Fiji open source software (version 2.0.0-rc-69/1.52i)
DAVID 6.8 web tool
GraphPad Prism (versions v7.05, v6.04, v8.02, or v8.04)
Image-Pro v7.0
Harmony high-content analysis software v3.5 (Perkin Elmer, Revision 105159)
QuantStudio 7 Flex Real-Time PCR System and ABI 7900HT Detection 480 System (both are from Applied Biosystems)
Proteome Discoverer software (ThermoFisher Scientific, v2.3.0.523)
hybrid human-bovine database (UniProtKB/Swiss-Prot version of January 2019)
Mascot (Matrix Science, version 2.6.0)
Cleaned peptides were separated on a nanoflow LC system (Thermo Scientific Dionex UltiMate 3000 RSLCnano)
IOX2 software (version 2.8.0.13 and 2.9.5.28, EMKA technologies, FR)
FACSDiva software v8
RTCA DA v1.0
Gpower v3.1.9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All data generated or analysed during this study are included in this published article. The scRNA-seq data are deposited on GEO at https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE148507 (ref: GSE148506, GSE148507 and GSE148504). source data for all graphically expressed figures are provided with the paper.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We designed the in vivo studies to ensure that minimum number of mice are used to obtain biologically significant results. For the mouse studies in Houston cohort, the sample size was estimated based on our previous study (https://pubmed.ncbi.nlm.nih.gov/24398018/) and we found that n= 8-10/group would be sufficient to give at least 40% biologically meaningful difference for the AF onset (the main readout) between groups for measured parameters with the power set at 80% and the level of significance at 5%. For the Montreal cohort of mice, sample size was estimated based on the results of a pilot studies performed prior to the main experiment; we found that a minimum of 15 (for AF duration) and 4-6 (for fibrosis) animals would be needed to achieve 8)% power with significance at 5%.
Data exclusions	No data was excluded from analysis.
Replication	Except for the RNAseq, microarrays and proteomic high-throughput profiling, the in vitro findings were successfully replicated in at least two independent experiments, or reproduced with additional methods throughout the manuscript: e.g., protein content - with immunoblotting, ELISA, scar-in-a-jar, colourimetric assays and immunostaining in numerous biological replicates; gene expression - with semi-quantitative PCR and real time quantitative PCR; cellular assays : cell proliferation - with BrDU and impedance-based assays; collagen content - with HPA, scar-in-a-jar and Sirius Red; in vitro studies were supported with complementary in vivo studies. Atrial fibrosis results in Montreal cohort were replicated in both sexes males and females; results on atrial fibrosis in Houston cohort were reproduced with different methods, i.e., sirius red and trichrome Masson's staining. More details are provided below. Fig.1. Data are pooled from individual donors assessed on the same day in one batch in single replicates (a, d-g), or (b-c, h-i) - in duplicates; all results are reproduced independently twice, or three times (a-c, j, k) in different subjects. Fig. 2. Data are pooled from individual donor cells assessed on the same day in single replicates except duplicates in (f, i-k). Data in (c) and (l)

were pooled from individual donor cells treated on 3 different days assessed on the same day in single replicates. All results were reproduced twice in different donors on different days, or for (a) and (b) - by different method in (g) and (h) respectively.
Fig. 3. Data are pooled from individual donor cells (a-f) treated on the same day and assessed in single replicates on the same day in one batch apart from (g) – assessed over 2-year period. The (e-f) were reproduced twice, except (g) - 3 times in different donors by different experimenters; data in (a) were partially reproduced by other methods (Fig.2a, 2e; Extended Data Fig.2a, 2e). Proteomic analysis was performed in single replicates following validation of reproducibility for (c) in duplicates (see Extended Data Fig.8j).
Fig.4. Data are pooled from individual animals assessed in single replicates on the same day in one batch. Data in (a-c) and (l-m) are pooled from 6-9 sections per animal stained on different days and assessed in one batch. Results in (a-c) were reproduced in another batch of animals by different lab using different method, or by another experimenter using different method (l-m); results in (6i) were repeated on two different days in the same animals. Results in (d-h) and (i-j, l-r) were obtained from individual animals over 2.5-years and 4-month period respectively.
Extended Data Fig.1. Data are pooled from individual donors assessed in single replicates (a, b, f, g-k, m, o-s) or duplicates (c-e, l, n); all results were reproduced independently twice.
Extended Data Fig.2. Data are pooled from individual donor cells assessed in single replicates, except duplicates (a-b, g, i), on the same day in one batch. Results were reproduced twice (a-c, f-h) in different donors. Data in (l-o) are pooled from 6 individual donors in sinus rhythm assessed in 14742 cells (post QC after filtering the initial 18466 total cellular barcodes) on the same day in one batch.
Extended Data Fig.3. The original data in (e) used for the GO analysis were pooled from 6 individual donors assessed in single replicates on the same day in one batch. Data are pooled from individual donors (l), or separate days (m-n) and assessed in single replicates on the same day in one batch apart from (n, single replicates on two different days), or in duplicates in (g, i, k) assessed on the same day. Findings in (a-d, j) were validated by another method (Fig.3a-b, g, Extended Data Fig.6b). All (except e) were reproduced twice in different donors.
Extended Data Fig.4. Data are pooled from 268 single cells isolated from 8 individual donors; scRNA-seq workflow was performed on the same day in one batch.
Extended Data Fig.5. The original data used for the analysis are pooled from 268 single cells isolated from 8 individual donors; the scRNA-seq workflow is carried out on the same day in one batch.
Extended Data Fig.6. Data in (a) are pooled from individual donors assessed in single replicate on the same day; results were reproduced in the same donors twice. Data in (b) are pooled from individual donors (a few cells in each field as shown in the figure) collected over two-year period, assessed on separate days and validated by 3 independent experimenters.
Extended Data Fig.7. Data are pooled from individual animals assessed in single replicates on the same day and reproduced in two centres in (a, c-d). Results in (m-n) were obtained from individual animals over ~2.5 years.
Extended Data Fig.8. Data in (a-c) are representative images of cells stained on the same day and reproduced three times on three separate days. Data are pooled from individual cultures assessed in duplicates (d), or from technical triplicates (g-h) and technical duplicates (i) analysed on the same day. Blots in (f) were reproduced twice in different donors.

Randomization

The Montreal mouse studies were not formally randomized, since the groups were determined by breeding rather than by intervention. The mice were studied consecutively as soon as they reached maturity upon breeding. All experimental studies (e.g., in vivo electrophysiology studies, qPCR, echocardiography and assessment of atrial fibrosis) were blinded to mouse genotype.
The Houston mouse studies were performed in mice of the same genotype - LKB1 FL/FL. Pups from same litter and same cage were injected as early as day-5 with the same virus and the males/females were separated at the time of weaning. Subsequently, litters were randomly allocated to each group, keeping overall numbers of mice for all the groups similar.

Blinding

For in vivo studies, genotype was not disclosed to the investigators performing data collection and those generating quantitative readouts. Experimenters were blinded to the group allocation during data collection and analysis (Montreal and Houston cohorts).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Calcitonin Receptor AHP635, Bio-Rad, UK, 1/500
BMP1 ab38953, Abcam, UK, 1/1000
COL1A2 (C-19) sc-8786, Santa Cruz Biotechnologies, USA, 1/1000
α-Smooth Muscle Actin A5228, Sigma, USA, 1/1000
p44/42 MAPK (Erk1/2) 9102S, Cell Signaling, USA, 1/1000
Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) 9101S, Cell Signaling, USA, 1/1000
Filamin A MAB1680-C, Merck, USA, 1/1000
Pro-calcitonin 130-00025-500, RayBiotech, USA, 1/1000
GAPDH-HRP-conjugated G9295, Sigma, USA, 1/1000

GAPDH MAB374, Millipore , USA, 1/1000
Calcitonin ab8553, Abcam, UK, 1/1000
αCGRP ab189786, Abcam, UK, 1/1000
CREB (E306) ab32515, Abcam, UK, 1/1000
PKA R2 (phospho S96) ab226754, Abcam, UK, 1/1000
PKA C alpha AF4268-SP, R&D Systems, UK, 1/1000
Cyclic-AMP MAB2146-SP, R&D Systems, UK, 1/1000
EPAC1 (5D3) 4155S, Cell Signaling, USA, 1/1000
EPAC2 (D3P3J) 43239S, Cell Signaling, USA, 1/1000
Collagen-1 C2456, Sigma, USA, 1/100
Fibronectin F3648, Sigma, USA, 1/1000
TotalSeq™-A0251 anti-human Hashtag 1 394601 BioLegend 1 µg/ml
TotalSeq™-A0252 anti-human Hashtag 2 394603 BioLegend 1 µg/ml
TotalSeq™-A0253 anti-human Hashtag 3 394605 BioLegend 1 µg/ml
TotalSeq™-A0254 anti-human Hashtag 4 394607 BioLegend 1 µg/ml
TotalSeq™-A0257 anti-human Hashtag 7 394613 BioLegend 1 µg/ml
TotalSeq™-A0258 anti-human Hashtag 8 394615 BioLegend 1 µg/ml
TotalSeq™-A0259 anti-human Hashtag 9 394617 BioLegend 1 µg/ml
TotalSeq™-A0263 anti-human Hashtag 13 394625 BioLegend 1 µg/ml
TotalSeq™-A0264 anti-human Hashtag 14 394627 BioLegend 1 µg/ml
TotalSeq™-A0260 anti-human Hashtag 10 394619 BioLegend 1 µg/ml
TotalSeq™-A0255 anti-human Hashtag 5 394609 BioLegend 1 µg/ml
TotalSeq™-A0256 anti-human Hashtag 6 394611 BioLegend 1 µg/ml.

Validation

Calcitonin Receptor AHP635 https://www.bio-rad-antibodies.com/polyclonal/rat-calcitonin-receptor-antibody-ahp635.html?f=purified
BMP1 ab38953 https://www.abcam.com/bmp1pcp-antibody-ab38953.pdf
COL1A2 (C-19) sc-87 86 https://www.scbt.com/p/col1a2-antibody-c-19
α-Smooth Muscle Actin A5228 https://www.sigmaaldrich.com/catalog/product/sigma/a5228
p44/42 MAPK (Erk1/2) 9102S https://www.cellsignal.com/products/primary-antibodies/p44-42-mapk-erk1-2-antibody/9102
Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) 9101S https://www.cellsignal.com/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-antibody/9101
Filamin A MAB1680-C https://www.sigmaaldrich.com/catalog/product/mm/mab1680c?lang=en&region=GB
Pro-calcitonin 130-00025-500 https://www.raybiotech.com/rabbit-anti-human-calcitonin-en-2
GAPDH-HRP-conjugated G9295 https://www.sigmaaldrich.com/catalog/product/sigma/g9295
GAPDH MAB374 https://www.merckmillipore.com/GB/en/product/Anti-Glyceraldehyde-3-Phosphate-Dehydrogenase-Antibody-clone-6C5,MM_NF-MAB374
Calcitonin ab8553 https://www.abcam.com/calcitonin-antibody-ab8553.html
αCGRP ab189786 https://www.abcam.com/cgrp-antibody-ab189786.html
CREB (E306) ab32515 https://www.abcam.com/creb-antibody-e306-ab32515.html
PKA R2 (phospho S96) ab226754 https://www.abcam.com/pka-r2pkr2-phospho-s96-antibody-ab226754.html
PKA C alpha AF4268-SP https://www.rndsystems.com/products/human-mouse-rat-pka-calpha-antibody_af4268
Cyclic-AMP MAB2146-SP https://www.rndsystems.com/products/camp-antibody-250532_mab2146
EPAC1 (5D3) 4155S https://www.cellsignal.com/products/primary-antibodies/epac1-5d3-mouse-mab/4155
EPAC2 (D3P3J) 43239S https://www.cellsignal.com/products/primary-antibodies/epac2-d3p3j-rabbit-mab/43239
Collagen 1 C2456 https://www.sigmaaldrich.com/catalog/product/sigma/c2456
Fibronectin F3648 https://www.sigmaaldrich.com/catalog/product/sigma/f3648
TotalSeq™-A0251 anti-human Hashtag 1 394601 https://www.biolegend.com/en-us/products/totalseq-a0251-anti-human-hashtag-1-16080
TotalSeq™-A0252 anti-human Hashtag 2 394603 https://www.biolegend.com/en-us/products/totalseq-a0252-anti-human-hashtag-2-antibody-16081
TotalSeq™-A0253 anti-human Hashtag 3 394605 https://www.biolegend.com/en-us/products/totalseq-a0253-anti-human-hashtag-3-antibody-16084
TotalSeq™-A0254 anti-human Hashtag 4 394607 https://www.biolegend.com/en-us/products/totalseq-a0254-anti-human-hashtag-4-antibody-16086
TotalSeq™-A0257 anti-human Hashtag 7 394613 https://www.biolegend.com/en-us/products/totalseq-a0257-anti-human-hashtag-7-antibody-16090
TotalSeq™-A0258 anti-human Hashtag 8 394615 https://www.biolegend.com/en-us/products/totalseq-a0258-anti-human-hashtag-8-antibody-16092
TotalSeq™-A0259 anti-human Hashtag 9 394617 https://www.biolegend.com/en-us/products/totalseq-a0259-anti-human-hashtag-9-antibody-16093
TotalSeq™-A0263 anti-human Hashtag 13 394625 https://www.biolegend.com/en-us/products/totalseq-a0263-anti-human-hashtag-13-antibody-16096
TotalSeq™-A0264 anti-human Hashtag 14 394627 https://www.biolegend.com/en-us/products/totalseq-a0264-anti-human-hashtag-14-antibody-16097
TotalSeq™-A0260 anti-human Hashtag 10 394619 https://www.biolegend.com/en-us/products/totalseq-a0260-anti-human-hashtag-10-antibody-16094
TotalSeq™-A0255 anti-human Hashtag 5 394609 https://www.biolegend.com/en-us/products/totalseq-a0255-anti-human-hashtag-5-antibody-16088
TotalSeq™-A0256 anti-human Hashtag 6 394611 https://www.biolegend.com/en-us/products/totalseq-a0256-anti-human-hashtag-6-antibody-16089.
In addition we have also performed in-house validation of the antibodies against pro-CT and CTR (as shown in the manuscript in Extended Data Fig.8b-d, g) using appropriate negative and positive controls, or HEK293cells stably overexpressing full length non-tagged human CTR (Extended Data Fig.8e-f), or using Locked Nucleic Acid-antisence oligonucleotides to knockdown the CTRs (Extended Data Fig.8c, Extended Data Fig.1l-m).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	All functional experiments were carried out in primary cells. The following cell lines were used as positive or negative controls during internal antibody validation steps with immunoblotting or real time qPCR: TT cell line ((#CRL-1803, ATCC) obtained from a 77 year old female patient suffering with medullary thyroid carcinoma; HEK293 cells (#CRL-1573, ATCC), human adult dermal fibroblasts (HDFa; #C-0135C, Gibco, Invitrogen cell culture, USA) and HEK293 stably expressing full length non-tagged human CTR (#P30136, Innoprot, USA).
Authentication	Authentication of cell lines was carried by the manufacturer as outlined below: ATCC CRL-1803 - https://www.lgcstandards-atcc.org/products/all/CRL-1803.aspx?geo_country=gb#specifications; ATCC CRL-1573 - https://www.lgcstandards-atcc.org/products/all/CRL-1573.aspx#specifications; Gibco C-0135C - https://www.thermofisher.com/order/catalog/product/C0135C#/C0135C; Innoprot P30136 - https://innoprot.com/product/hitseeker-calcitonin-receptor-cell-line/ In-house cell authentication was performed by monitoring cell morphology and phenotypical tests (e.g., immunostaining and flow cytometry - for CTR protein and ELISA - for CT secretion). Cell lines were certified by the manufacturer.
Mycoplasma contamination	Tested negative using immunofluorescence staining with DAPI (as shown in the manuscript, Fig. 2a, Fig.3g, Extended Data Fig.6b, 8b-d).
Commonly misidentified lines (See ICLAC register)	None.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Animal studies were carried out in mice; age: 10-12 weeks old; gender: males and females; genetic background: CMV CRE https://www.jax.org/strain/006054, LKB1 FL/FL https://www.jax.org/strain/014143, CTR flox , B6.129-Calcrtm1Rda/Apb (generated by Prof RA Davey, University of Melbourne). Housing conditions: The CTR-KO and control mice (Montreal cohort) were housed in Allentown XJ cages at 20-22°C, 50% humidity and 60 air changes/hour ventilation conditions. Diet consisted of the sterilized food (#2019S, Envigo) and osmotic water. The CTR-KO and control mice (Melbourne cohort) were housed in a specified pathogen-free facility at 22°C, in a 12-hour light/dark cycle and were supplied with standard irradiated mouse chow (1.2% calcium and 0.96% phosphorus; Ridley Agriproducts, Western Australia) and water ad libitum. Breeding mice were housed in micro-isolator cages and offspring used for experiments were transferred to open-top cages at weaning (3–5 mice/cage). Cages contained corn-cob bedding, and cardboard tubes and tissues were supplied for environmental enrichment. Studies in LKB1-KD, LKB1/CT-dKD, LKB1-KD+CT and controls (Houston cohort) were housed in standard mice cages provided with the bags of sizzle net as cage enrichment and were fed standard feeder chow as approved by the IACUC and recommended by 'the Guide' (NIH Publication #85-23, revised 1996).
Wild animals	We did not use wild animals.
Field-collected samples	We did not use field-collected samples.
Ethics oversight	All animal work was performed in accordance with the local Montreal Heart Institute and Austin Health Animal Care and Ethics Committee Ethics oversight guidance and in accordance with NIH guidelines. Studies in LKB1-KD, LKB1/CT-dKD, LKB1-KD+CT and controls (Houston cohort) were performed according to protocols approved by the Institutional Animal Care and Use Committee (IACUC) at the Baylor College of Medicine.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patients (n=156 in total) undergoing coronary artery bypass grafting (CABG) and/or valve surgery in the John Radcliffe hospital, Oxford (UK). Detailed patients' characteristics are summarized in the Extended Data Table 1 of the manuscript. All patients gave informed written consent. Right atrial biopsies were collected before cardiopulmonary bypass, rinsed of any blood contamination and immediately processed for cell isolation or snap-frozen until use.
Recruitment	Patients were recruited according to the approved study protocol, i.e., via face-to-face communication with a trained researcher; every recruited participant signed a consent form which is safely stored securely. All patients admitted to the John Radcliffe hospital for cardiac surgery were eligible for this study, unless they: (1) underwent previous cardiac surgery, (2) younger 18 or older 85 years of age, and (3) are not able/not willing to consent. Clinical characteristics of the participants were derived from medical notes. There were no self-selection bias or other biases during patients recruitment.
Ethics oversight	Studies involving human participants were approved by the local Research Ethics Committee (South Central - Berkshire B Research Ethics Committee, UK; ref: 18/SC/0404 and 07/Q1607/38).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For flow cytometry was used to validate anti-CTR antibody used in the study. We used HEK293 cells stably expressing full length non-tagged human CTR (#P30136, Innoprot, USA). The cells were sub-cultured according to the manufacturer instruction, gently trypsinised and stained with the anti-CTR antibody or IgG control using standard staining protocol. Cells were kept on ice through the preparation process and until flow cytometry.
Instrument	Becton Dickinson (BD) FACS Aria Fusion III sorter.
Software	BD FACSDiva v8.0
Cell population abundance	Highly abundant HEK293 cells positive for human CTRs.
Gating strategy	Cells were gated for viable (based on DAPI_negative signal) singlets (standard gating strategy) as shown in the Extended Data Fig. 8ef

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.