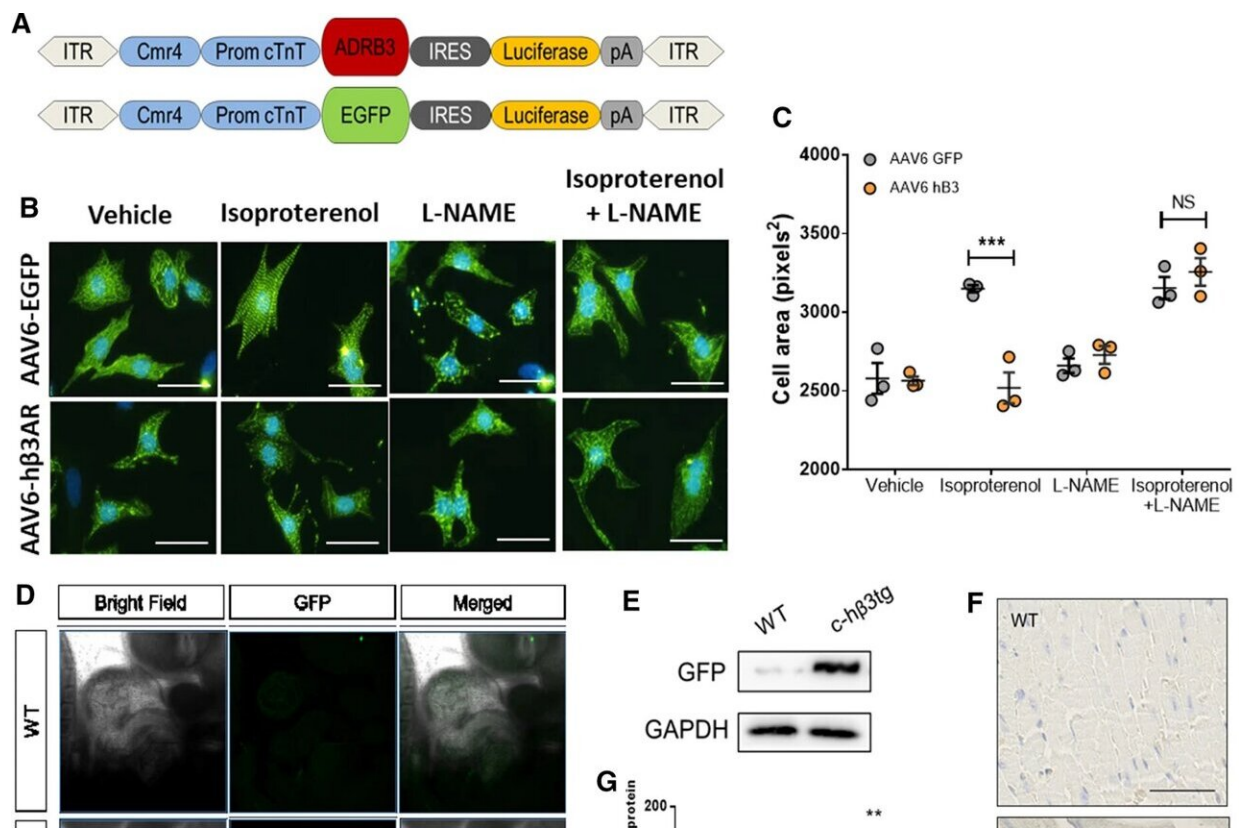


# A new therapeutic target for the prevention of heart failure due to aortic stenosis

November 30 2022



Cardiomyocyte-specific human  $\beta$ 3AR overexpression prevents cardiomyocyte hypertrophy upon catecholamine challenge via NO/cGMP pathway. **A** Genetic constructs for adeno-associated virus (AAV) vectors encoding h $\beta$ 3AR and control EGFP. ITR, recognition site for AVV packaging; Cmr4, enhancer sequence; Prom cTnT, troponin T promoter sequence for cardiomyocyte-specific expression; ADRB3, human  $\beta$ 3AR receptor cDNA sequence, *EGFP* enhanced green fluorescent protein sequence, *IRES* internal ribosome entry site, Luciferase, firefly luciferase sequence; pA, simian virus 40 polyadenylation

signal. **B** Representative images of neonatal rat ventricular myocytes (NRVM) transduced with control (AAV6-EGFP) or human  $\beta$ 3AR adeno-associated virus (AAV6-h $\beta$ 3AR) for 72 h and incubated for 24 h with isoproterenol (10  $\mu$ M), L-NAME (100  $\mu$ M) or both. Nucleus is stained in blue with DAPI and  $\alpha$ -actin is stained in green to differentiate myocytes from other cells. Scale bar, 60  $\mu$ m. **C** Size assessment of NVRM treated as above (40 cells/condition in each preparation; 3 independent preparations). The isoproterenol-induced hypertrophic response is blunted in h $\beta$ 3AR myocytes and NOS inhibition by L-NAME restores the hypertrophy. **D** Confocal microscopy images of E9.5 *cTnT<sup>+/+</sup>;R26ADRB3<sup>tg/tg</sup>* (control) and *cTnT<sup>Cre/+</sup>;R26ADRB3<sup>tg/tg</sup>* (c-h $\beta$ 3tg) embryos, showing cardiac expression of GFP in an E9.5 embryo. **E** Immunoblot showing GFP expression in cardiomyocytes isolated from adult c-h $\beta$ 3tg mice. **F** Immunostaining analysis for GFP in cardiac tissue. Scale bar, 50  $\mu$ m. **G**  $\beta$ 3AR protein levels is increased in c-h $\beta$ 3tg mice.  $\beta$ 3AR density (Bmax) in fmol of [3H]-CGP12177 specifically bound/ mg protein in homogenates from c-h $\beta$ 3tg (red,  $n = 3$ ) and WT (black,  $n = 3$ ) hearts. **H** Mice with cardiomyocyte-specific overexpression of human  $\beta$ 3AR (c-h $\beta$ 3tg, red) and littermate controls (WT, black) were subjected to transaortic constriction (TAC) surgery (to induce supravalvular AS) or sham surgery and were followed for 2 weeks. **I** Supravalvular AS was confirmed by echocardiography as an increase in the descendant aortic velocity blood flow. **J** ATP levels were increased in hearts from c-h $\beta$ 3tg 2 weeks after supravalvular AS induction ( $n = 5$ /condition). **K** Cyclic GMP:AMP levels ratio was boosted in hearts from c-h $\beta$ 3tg mice, thus suggesting an enhancing effect of human  $\beta$ 3 overexpression in cardiomyocytes on NO/cGMP signaling ( $n = 5$ /condition). Data are means  $\pm$  SEM. Mann–Whitney or Student’s *t* test for non-normally or normally distributed data, and Kruskal–Wallis test with Dunn’s multiple comparisons test. \**p*

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