ALTERED GENE EXPRESSION IN KLF13 NULL HEARTS

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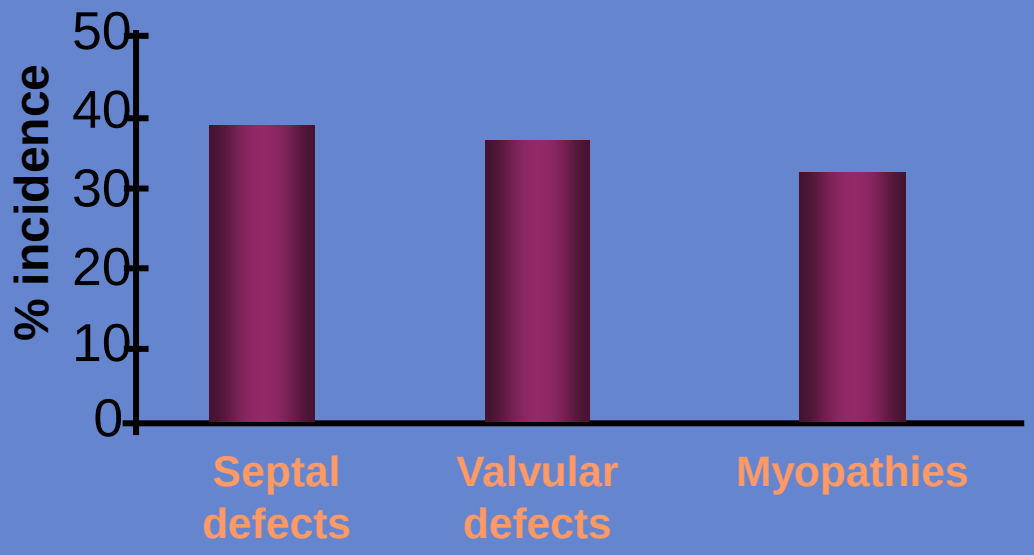
Congenital Heart Disease

1% of live birth

25% of congenital defects

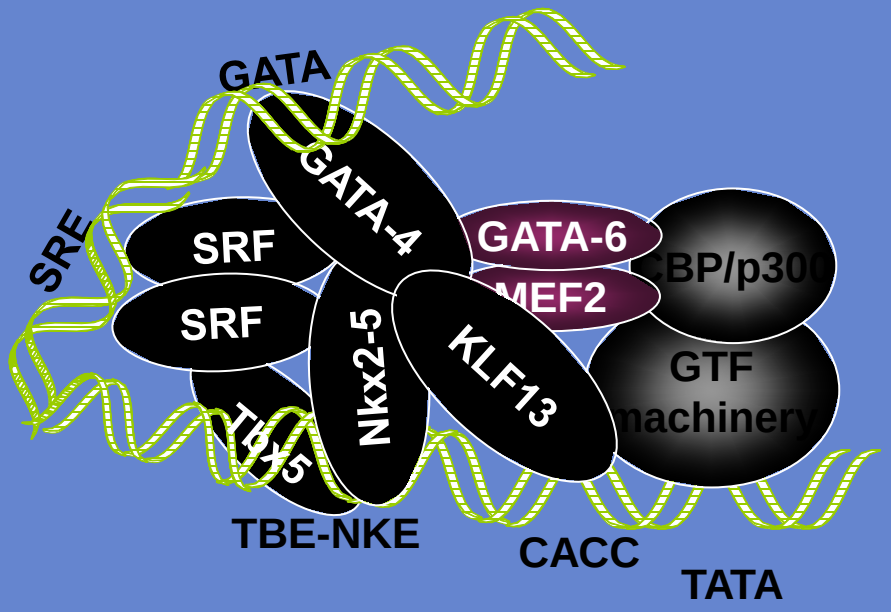
Leading cause of death in infants under 1 year of age

Major risk factor for premature cardiovascular complications in adults



Transcriptional regulation of heart development is a multipartner affair: 1 phenotype= several genes (eg. Role of Nkx2.5, Tbx5 and GATA4 in atrial septal defect (ASD))

Complex interactions between transcription factors to regulate gene expression during cardiac development



KLF13 is so far identified as a partner for : GATA4, Tbx5, Nkx2.5, Znf246

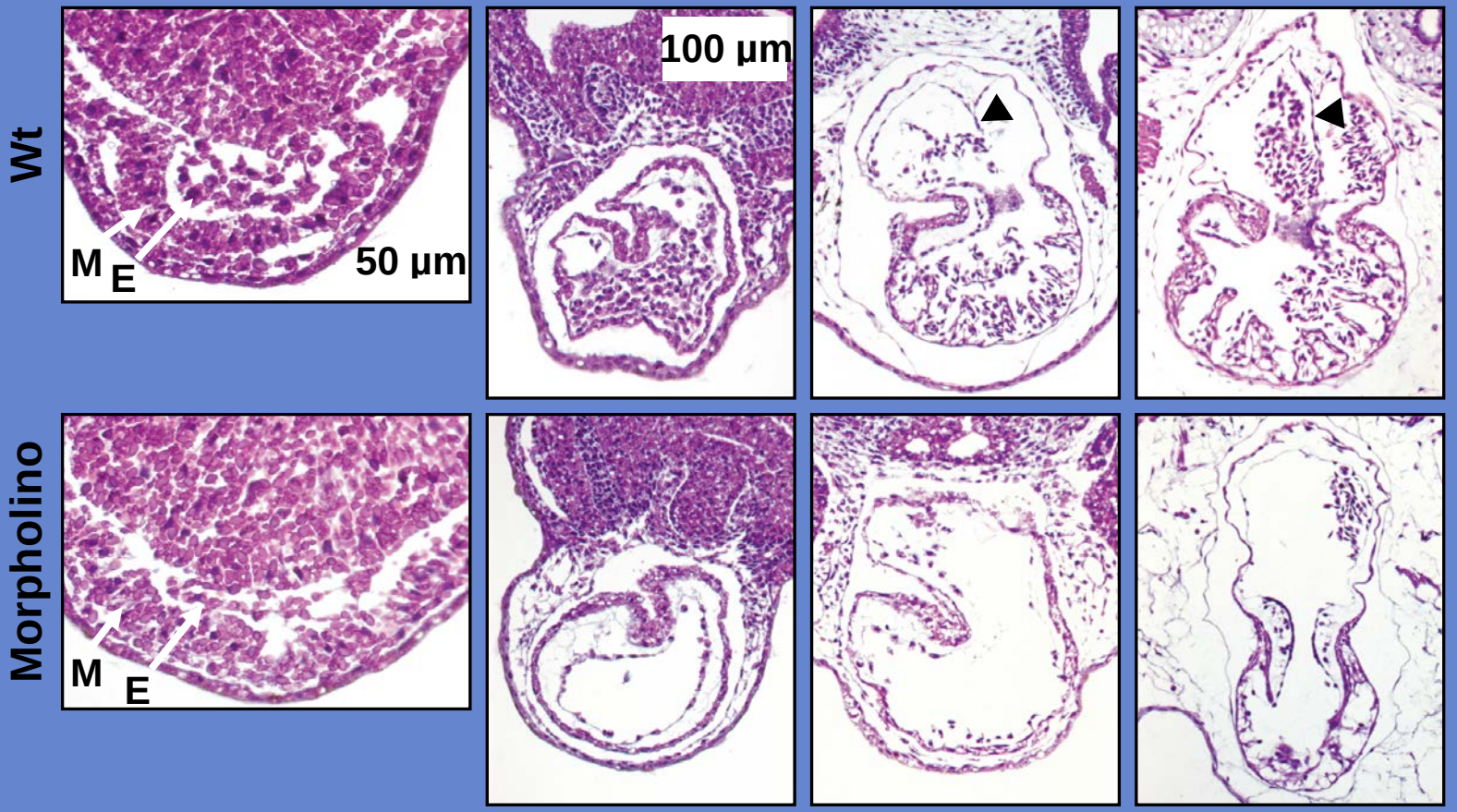
KLF13 interacts with several cardiac transcription factors and is part of a multiprotein cardiac enhanceosome

What we know about KLF13?

- KLF13 exists as 2 isoforms with distinct biochemical properties
- KLF13 is a critical regulator of the cardiac genetic program
- KLF13 is expressed in the developing heart and is reduced substantially postnatally.
- KLF13 transactivates multiple cardiac promoters, synergistically with GATA-4
- KLF13 expression was detected in the heart, thymus, dermis, skeletal muscles and epithelial layers of the gut and the urinary bladder.

Klf13 is a candidate Congenital Heart Disease causing gene in human

Depletion of KLF13 leads to hypotrabeculation and septation defects in Xenopus



Lavallé G et al., *The Kruppel-like transcription factor KLF13 is a novel regulator of heart development*, EMBO , 2006 Nov 1.

What would be the cardiac phenotype in KLF13 Knock-out mice?

Strategy used to knock-out KLF13 in mice

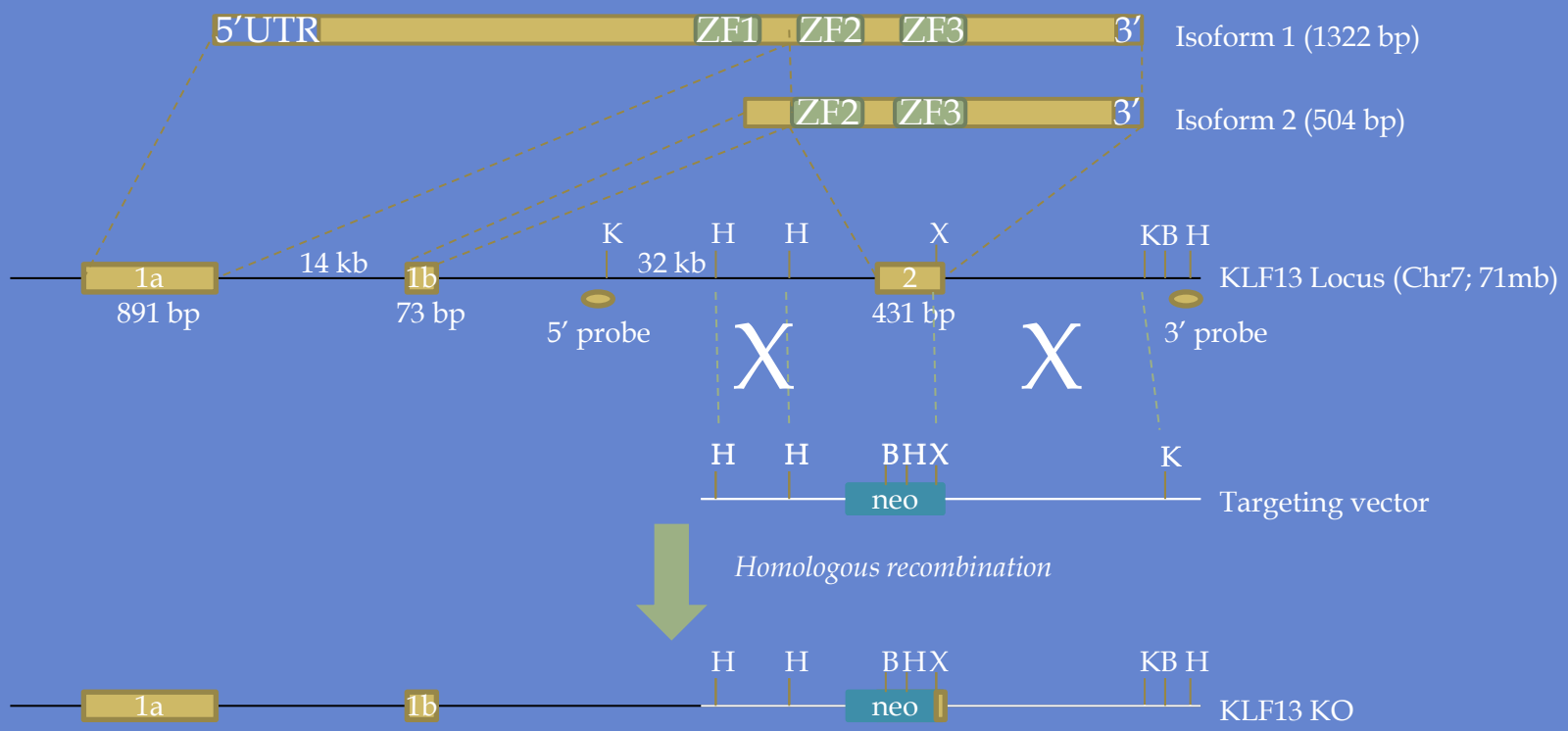


Figure 1
Schematic representation of the KLF13 locus and targeting strategy.

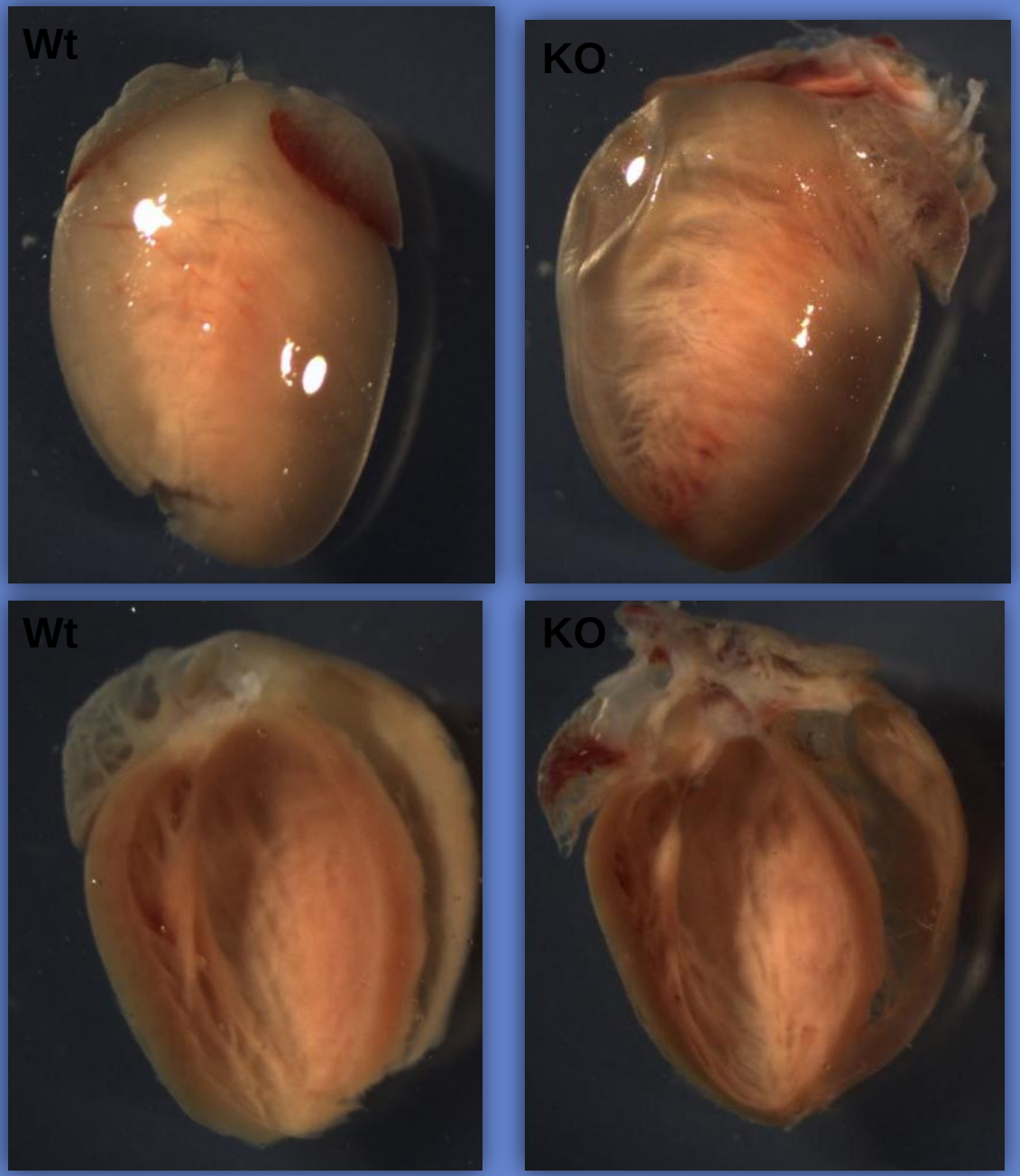
Klf13-/-

Viability of KLF13 Null mice

	Genotype		
	Wt	Wt/KO	KO
Expected	25%	50%	25%
Obtained	31.6%	54.5%	14.0%

KLF13 Null Mice have reduced viability and multiple cardiac phenotypes

Dilated Right Ventricle in KLF13 null mice



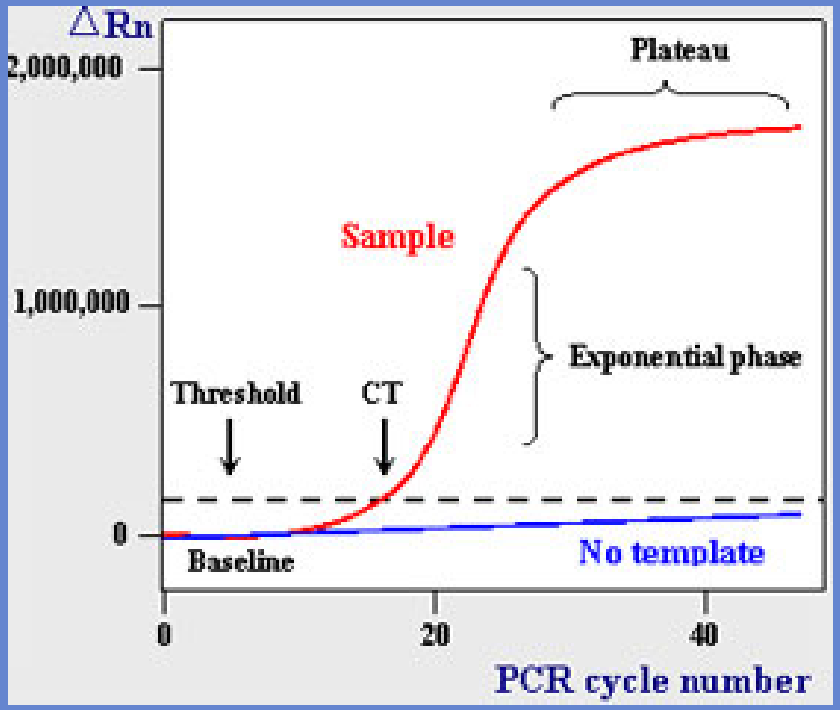
My project

Objective: determine the gene expression profile in KLF13 knock-out mice compared to their heterozygous counterpart.

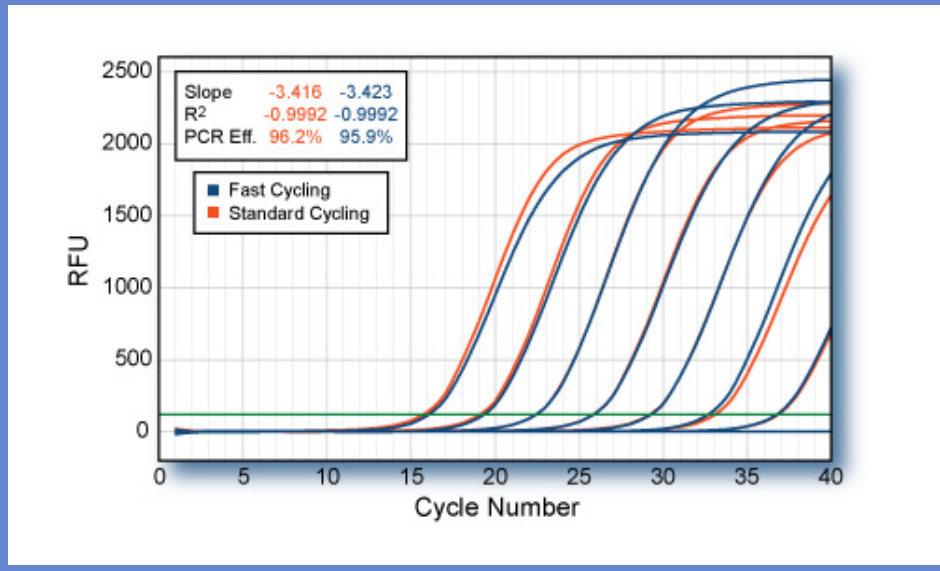
More specifically, comparing the gene expression between the left and the right side of the heart

Hypothesis: KLF13 is important in mammalian cardiac development, particularly in the right side of the heart.

Method: Real Time PCR



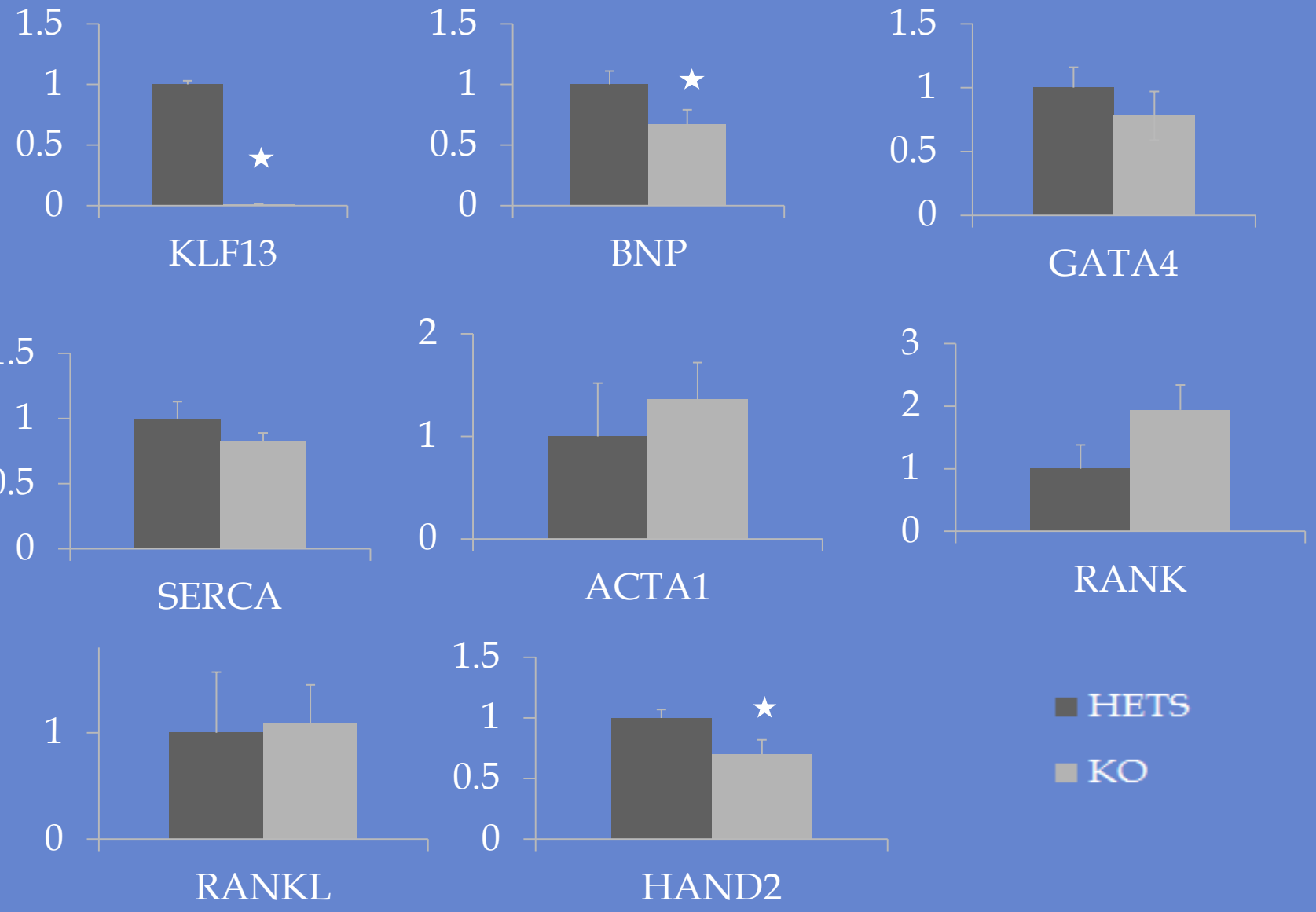
http://www.nem.wur.nl/UK/education/Other+courses+1/Molecular+Identification/



http://www.quantabio.com/lightbox.php?performance_id=62

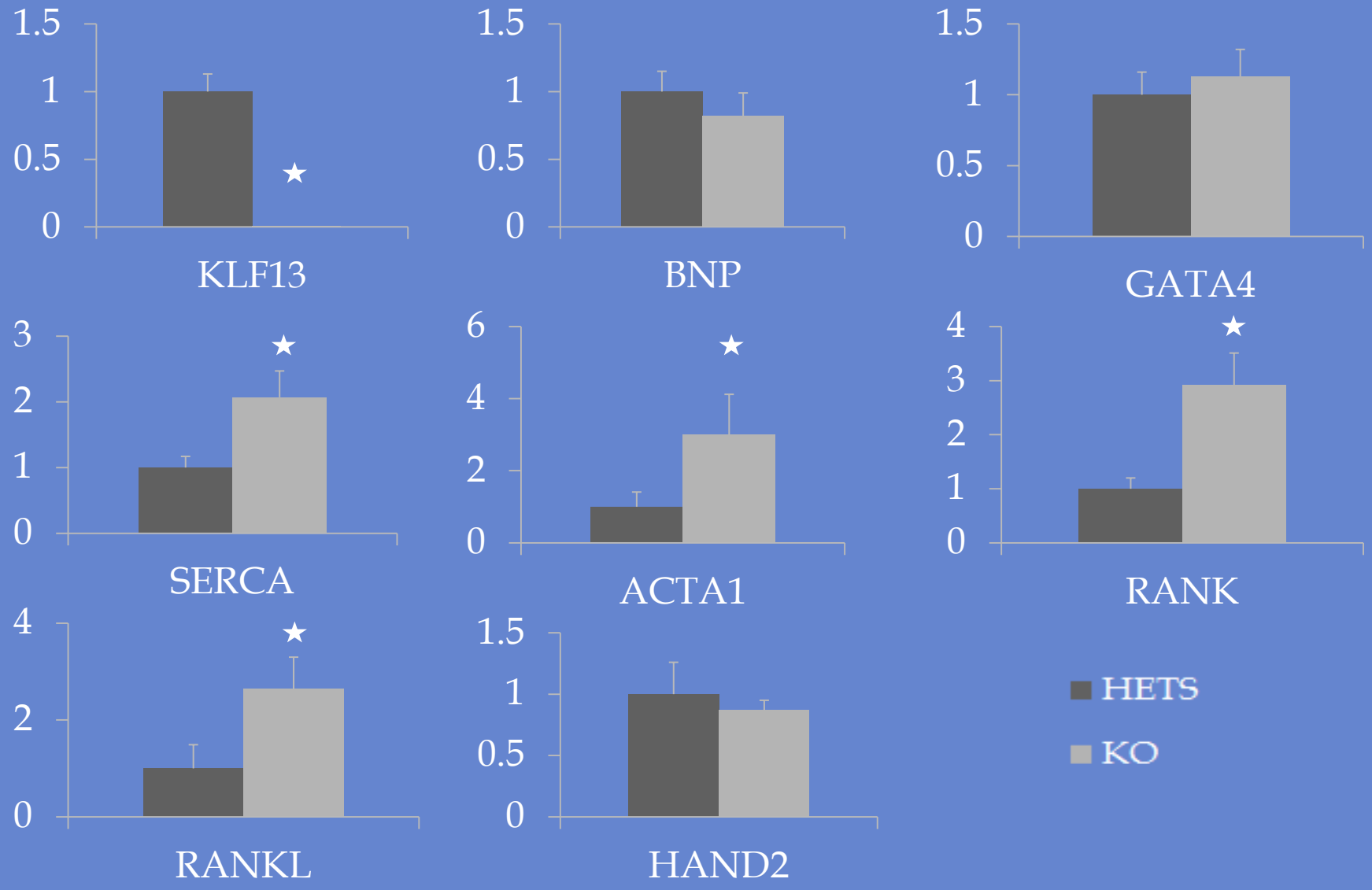
Amplify and simultaneously quantify a targeted DNA molecule

Gene expression profiling in the Left Ventricle of Klf13 -/- mice



BNP and HAND2 are down-regulated in the left ventricle

Gene expression profiling in the Right Ventricle of our model mice



SERCA, ACTA1, RANK and RANKL were upregulated in the right ventricle and not in the left ventricle.

Conclusion

Our KLF13 knock-out mice have a reduced viability, confirming the importance of KLF13 in mammalian cardiac development. However, the surviving KLF13 null mice seem to have a problem in the right side of the heart.

The comparative gene expression profiling in the right and left ventricles supports our hypothesis concerning the important role of KLF13 in the right heart.