

***PRDM16* - a Novel Key Player in Cardiomyopathy**

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We recently identified a nonsense mutation in the transcriptional co-factor *PRDM16* (PR domain containing 16) resulting in left ventricular non-compaction (LVNC) and dilated cardiomyopathy in human patients. To establish a personalized disease model for the latter, we faithfully recapitulated the LVNC by cardiomyocyte-specific overexpression of both mutant and wild-type (WT) *PRDM16* in zebrafish. We observed an impaired cardiomyocyte proliferation with associated physiologic defects in cardiac contractility and cell-cell coupling during development in mutant but not WT *PRDM16* zebrafish and these defects persisted throughout adulthood. In a next step, using a phenotype-driven screening approach in the fish, we identified a melanocortin 4 receptor (MC4R) antagonist that rescued the physiologic defects associated with mutant *PRDM16* during development. In addition, this compound also attenuated the contractile- and electrical defects observed in *PRDM16* mutants. Of note, MC4R antagonists could also rescue the cardiac defects seen in zebrafish models of arrhythmogenic right ventricular cardiomyopathy (ARVC) which is consistent with our observation that *PRMD16* is also mutated in ARVC patients. While future studies to further elucidate the exact mechanism of mutant *PRDM16*-related cardiomyopathy are warranted, our current findings underline the importance of personalized disease models. Indeed, such an approach to investigate the aberrant activation of specific pathways, would greatly accelerate the exploration of disease biology and facilitate the development of innovative tailor-made therapies.