**Call for Young talent grant**
**CVON DOSIS/ARENA PRIME**

In the framework of the Dutch CardioVascular Alliance (DCVA) CVON DOSIS and CVON ARENA PRIME are together putting out a call for Young Talents to allow them to apply for funding for innovative and insightful research related to cardiomyopathies. The grant will provide up to 50k euro to be spend on a 9-12 month research project. During this period the hostlab is expected to provide additional funds to match the salary/benchfee. National applicants are stimulated to explore opportunities to perform their research abroad, although the proposed research can also be performed in their current labs. All (inter)national postdocs or PhD students are eligible to apply.

The proposal needs to adhere to the provided proposal template and the submission deadline will be May 1st. The proposal and a letter of commitment from the host institute should be submitted to: info@heart-institute.nl
An expert panel of outside reviewers will select the top 4 proposals, and the 4 selected candidates are invited to pitch their proposal at the upcoming 4th Translational cardiovascular research meeting in Utrecht on June 25-26 (https://congress2020.heart-institute.nl). Two proposals will be selected for funding.

Awardees are expected to participate and present their progress during CVON DOSIS or CVON ARENA-PRIME network meetings.

**CVON DOSIS**
**Coordinators:** Prof J van der Velden and Prof. RA de Boer

**Summary:** Inherited cardiomyopathies (CM) are clinically highly variable and show age-dependent and variable penetrance, i.e age of onset in patients with the same mutated gene can vary from early age to senescence. But even for a given mutation in one gene, onset and disease severity largely differ implying that additional determinants, including genetic variations, environmental and/or toxic disease triggers, and an age-related decline in protective mechanisms (protein quality control (PQC) system) impede on disease susceptibility. The PQC system prevents derailment by sequestering the mutant protein and subsequent toxic protein accumulation in the cardiomyocyte. Moreover, derailment is attenuated by the stimulation of protein degradation pathways, including autophagy. Thus, a healthy PQC system keeps mutant expression below the toxic dose and prevents the pathogenicity and onset of cardiomyopathy. In addition to secondary disease factors, location of a specific mutation in a gene might determine disease susceptibility. We hypothesize that severity of functional and structural impairments and capability of the

PQC system to counteract the mutant protein depend on specific mutation-induced changes in protein structure.
We aim to I) identify additional genetic and environmental mechanisms responsible for increased expression and toxicity of mutant protein during ageing, to uncover the role of derailed PQC system in CM and test whether boosting of PQC counteracts disease onset and severity. In addition we aim to II) establish whether mutation location determines its expression by recognition by PQC, its incorporation in the sarcomeres and its functional consequences and finally test whether therapies to normalize the PQC system and increase contractile strength can prevent and/or delay mutation-induced defects of the heart muscle.

**CVON ARENA-PRIME**
**Coordinators:** Prof Y Pinto and Prof L de Windt

**Summary:** ARENA-PRIME is focussed on forms of HF that are resistant to current HF treatment. In previous decades, generally applied therapies substantially improved survival of HF patients. Still, in a minority of patients, these treatments fail to halt the progression of the disease. This particularly concerns younger patients with forms of dilated cardiomyopathy (DCM) or arrhythmogenic cardiomyopathy (ACM). ARENA-PRIME takes the individual disease mechanism of DCM caused by mutations in the *RBM20* and *LMNA* genes as well as ACM caused by mutations in the *DSGL2* and *PKP2* genes as forms of treatment-resistant HF to develop novel RNA therapies tailored to the individual disease.

We capitalize on the knowledge gained in ARENA on inhibitory RNAs to develop novel smart siRNAs to inhibit mutated alleles with just a few siRNAs, avoiding the need to generate an siRNA for each discrete mutation. We will use this technology to target the toxic allele that results from *LMNA* mutations to treat *LMNA*-DCM. Furthermore, we will investigate multiple innovative strategies to treat ACM caused by mutations in the *DSGL2* and *PKP2* genes with allele-specific short hairpin RNAs and antimiRs. These translational work packages are complemented with state-of-the-art delivery-technologies based on adeno-associated viral (AAV) vectors and antibody conjugation. We will also connect the national wealth of heart tissue collections to novel high-end sequencing- technologies like single-cell sequencing to further explore disease mechanisms. Finally, we will assess the clinical efficacy and specificity of the most optimal as-siRNA strategy in patients carrying the *LMNA* disease that will be included in the RNA therapy clinical trial proposed in ARENA-PRIME. Upon completion of this programme, we anticipate to have done a First In Man application of an inhibitory RNA and achieve *pre*clinical proof-of-concept of *DSGL2 and PKP2* directed therapies on their path towards clinical reality.