# THE HARTWELL FOUNDATION

## 2016 Individual Biomedical Research Award

**Jop van Berlo, MD, Ph.D.**

**Assistant Professor**
**Department of Medicine**

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**Unlocking the Regenerative Potential of the Heart**

Hypoplastic left heart syndrome (HLHS) is a debilitating form of congenital heart disease that affects 1 in 4,000 births and is responsible for 25% of deaths due to congenital heart defects. Children with HLHS have underdeveloped hearts with too few heart muscle cells (cardiomyocytes) to pump blood effectively throughout the body. Despite dramatic improvements in surgical treatment options, only 50 - 70% of affected children survive to five years of age and children that survive will suffer from neurocognitive delay and incapacitating physical limitations. Ultimately, children die prematurely as a result of heart failure because the diseased heart is unable to keep up with the demands of the entire body due to a lack of sufficient cardiomyocytes. Fortunately, there may be an opportunity to intervene and increase the number of these muscle cells, because cardiomyocytes in the heart of a young child still have the capability to divide and multiply. Effectively, by encouraging the ability of a juvenile heart to form additional new cells soon after birth might allow the heart to recover function and significantly improve clinical outcome. To identify target drugs that can increase the number of cardiomyocytes, Jop has performed a genome-wide screen and identified 266 novel candidate genes. Remarkably, many of the newly discovered genes have not been described before. Using live cell imaging of primary contractile cells, for which he is developing novel image analysis algorithms, Jop has observed that inhibition of certain genes stimulated cardiomyocyte proliferation (cell division) in culture. Based on his preliminary data, he now seeks to explore the mechanism and timing of the cell cycle and determine which of the 266 identified candidate genes has the greatest potential to increase the numbers of heart muscle cells inside the heart, *in situ*. With this information he will determine the therapeutic potential to increase cardiomyocyte numbers in his novel animal model of HLHS, a model he created by resecting the bottom part of a mouse heart one week after birth when contractile cells have stopped dividing. The HLHS animal model is based upon the fact that the heart cannot recover from this intervention and will develop a scar, reducing the number of contractile heart cells and thus mimicking the underdeveloped left ventricle present in children with HLHS. Jop will deliver the defined target drug(s) using a proprietary gel delivery system to precisely alter gene function in heart muscle cells. If Jop is successful, it will be possible to advance clinical translation and for the first time, offer children affected with HLHS a non-surgical intervention that will enable their undeveloped left ventricle to generate enough contractile force to pump blood effectively throughout their body, improving both their survival and quality of life.