# Growing ‘Mini Hearts’: The bid to find a Hypertrophy Cure

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## What is the problem?

Hypertrophic Cardiomyopathy (HCM) is a pathological condition that causes the heart’s muscle wall (known as the myocardium) to thicken due to an increase in size of the muscle cells. As a result, the heart cannot function correctly, through a lack of contractibility, ultimately causing cardiac arrest, which is frequently fatal (see Figure 1). There is currently no pharmaceutical therapy for HCM, although current management techniques include drugs which reduce blood pressure.

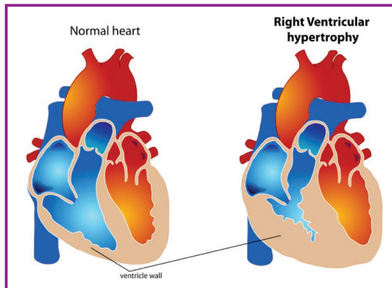


**Figure 1** depicts the heart of someone suffering from Hypertrophic Cardiomyopathy (HCM). Note the thickened muscle wall of the right ventricle, one of the four chambers of the heart.

Mariana Ruiz from https://commons.wikimedia.org/wiki/Main_Page

There is no obvious cause for the disease and sufferers may be unaware that they have the condition. Those most at risk are athletes in their early twenties, who often push themselves physically, promoting the condition. As many as 36% of cardiovascular deaths in athletes are due to HCM.

## What are we interested in?

Recent research has suggested the role of an enzyme called CDK9 as the cause of the abnormal increase in size (hypertrophy) of the heart muscle cells (known as cardiomyocytes) in HCM. We wanted to see if inhibiting CDK9 in an *in vitro* (in a vessel in the lab) model of the disease would reduce the heart muscle cells’ size, indicating that the enzyme is involved in the hypertrophic change. This might allow us to stop disease progression and evaluate the potential of the CDK9 inhibitor as a therapeutic treatment.

## What did we do?

One of the many challenges in medical research into HCM is finding participants of suitable criteria to study. Another issue is the delicate nature of heart tissue, which makes drug trials difficult. For this project, we used a new *in vitro* model of the condition instead of live subjects. We differentiated embryonic stem cells (which are cells derived from embryos that can be differentiated into lots of different cell types) into human heart muscle cells. These ‘mini hearts’ were kept in 96-well plates, so we could perform many tests on the hearts to get more data. They were around 1mm in length and beat independently.

We added compounds called Ang II and ET-1 to the ‘mini hearts’, which are known to cause hypertrophy in the cells and we also added a drug, known as “CYC202”, which inhibits CDK9. We looked at the effect of the drug on cell viability as well as the effect of different amounts of the three compounds, to see if CYC202 reduced the size of the cells or halted the progression of our HCM model.

## What did we find?

Our research showed that CYC202 prevented hypertrophy in our ‘mini hearts’ model of the disease as measured by ‘mini heart’ volume (see Figure 2). In some dosages of CYC202 we were able to reduce the volume of the ‘mini heart’ (see Figure 3).

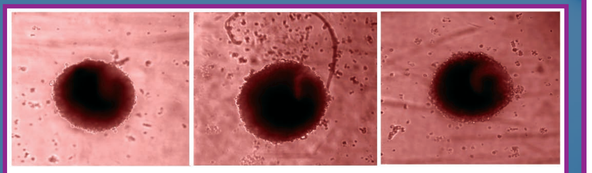

**Figure 2** shows A) a healthy untreated control ‘mini heart’; B) a ‘mini heart’ treated with Ang II and ET-1 to create hypertrophy; C) a ‘mini heart’ treated with Ang II, ET-1 and CYC202, which did not show Ang II and ET-1 induced hypertrophy.

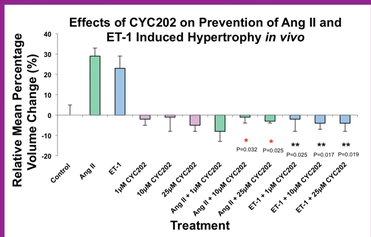


**Figure 3** shows the effect, in terms of the percentage change in volume, on our ‘mini hearts’ when various combinations and concentrations of Ang II, ET-1 and CYC202 were added to the ‘mini hearts’, compared to the control ‘mini hearts’, which were grown under normal growth conditions.

## What does this mean?

We have identified a compound that has stopped an *in vitro* model of HCM from progressing and provided evidence that CDK9 is involved in disease progression. We can use these findings as the basis for further investigating a possible therapy for the condition.

## Who am I?

I am in my final year of the BSc (Hons) Biomedical Science programme at Abertay University, Dundee and am interested in pathology. Thanks to Medical Research Scotland I have been able to gain invaluable experience in pathological research which has helped me appreciate the research process. The results of this study were presented as a poster to the Industrial Biotechnology Congress 2015 in Birmingham, and won the best poster award, and published in Lewis K, Reynolds L, Kuzmanova E, Zhelev N. ‘Evaluation of the therapeutic potential of a CDK9-inhibiting compound in human hypertrophic cardiomyopathy using hESC-derived cardiomyocytes.’ J Biotechnol Biomater 2015; Vol 5(2) p 64. I am now applying for a postgraduate research degree. I fully encourage others to consider a career in research as it enables you to realise advances within science as well as experience creative freedom and utilise techniques and knowledge you have accumulated over the years.

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Lewis was supervised during his Vacation Scholarship project, *“Evaluating the therapeutic potential of CDK9 inhibiting compounds in human hypertrophic cardiomyopathy using embryonic stem-cell-derived ‘mini-hearts’”*, by Professor Nikolai Zhelev.