

Novel Approaches for Treating Cardiac Disease

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Heart failure and cardiovascular disease (CVD) is number one worldwide killer of men and women, including the United States. On the basis of 2016 mortality data, CVD currently claims more lives each year than cancer and chronic lung disease combined. Globally, more than 17 million deaths in year 2016 were caused by CVD that was 14.5% more than year 2006, and it is expected to rise to >23.6 million deaths by year 2030. In the United States, nearly 1 in 3 deaths is accounted by the CVD. In year 2015, ~41.5% of the U.S. population had at least one CVD condition (www.cdc.gov), and The American Heart Association (AHA) estimates that by 2035, 45.1% of the US population would have some form of CVD. The prevalence of CVD in adults (≥ 20 years of age) is 48.0% and increases with age in both males and females. These numbers show that cardiac and related diseases are placing a heavy financial burden in the economy and the health care system. The total costs (direct and indirect treatment) of CVD in the USA continue to rise- in year 2016 it was \$555 billion and is expected to reach \$1.1 trillion in year 2035. Although there are several classes of drugs available to treat and prevent cardiac diseases, the 5-year survival rate is still only 50%.

Given these grim statistics it's even more dire given that currently no satisfactory treatment is available for heart failure, highlighting the critical need for more effective therapeutic strategies. The goal of our current research is to develop novel ways for deliver the neuropeptide α -calcitonin gene-related peptide (α CGRP) as a potential therapy for heart failure. Alpha-calcitonin gene related peptide (α -CGRP), a 37-amino acid regulatory neuropeptide, one of the most potent vasodilators known. Our laboratory and other research groups had established the protective function for α CGRP in various cardiac diseases, including heart failure, hypertension, and cardiac ischemia [1, 2]. In α CGRP knock-out mice, transverse aortic constriction (TAC) induced pressure-overload significantly exacerbates cardiac hypertrophy and subsequent dilation and dysfunction, cardiac fibrosis, and mortality [3]. Recently a α CGRP analogue was shown to protect against adverse cardiac remodeling and dysfunction caused by AngII-induced hypertension or abdominal aortic constriction-induced heart failure [4].

However, the short half-life of α -CGRP (~5.5 min in the human plasma) limits its use as a therapeutic agent in humans. Because of this critical hurdle, we have taken a two pronged approach towards treating heart failure. The present study is aimed to develop a novel α -CGRP agonist analogue with extended stability and efficacy in human plasma. First we have chemically synthesized a peptoid-peptide hybrid of α -CGRP by coupling a peptoid monomer *N*-methoxyethylglycine (NMEG) molecule to the N-terminus end of the human α -CGRP peptide (we termed it as NMEG- α CGRP) that we believe will be more stable in the body. Our *in vivo* data demonstrates that NMEG- α CGRP is a biologically active molecule as subcutaneous administration of NMEG- α CGRP lowers the blood pressure in wild-type mice. Additionally, NMEG- α CGRP exhibits no cellular toxicity when incubated with two different cardiac cell lines, rat H9C2 cells and mouse HL-1 cells Figure 1. The second prong is to use a new delivery system based on our previous work using alginate microcapsules to deliver cells or drugs to diseased tissues [5].

Similarly, α -CGRP encapsulated in alginate microparticles lowered the blood pressure in wild-type mice and exhibited no cellular toxicity when incubated with the same two cardiac cell lines Figure 2. We have both prongs submitted to for patent approval. Both treatments have now begun animal testing in our TAC model of heart failure and those results will be presented at the meeting. As both the alginate microcapsules and NMEG- α CGRP are non-toxic and possess hypotensive action, they are exciting potential therapeutic agents to treat and prevent various cardiovascular diseases, including, heart failure (pressure- as well as volume-overload), myocardial infarction, and hypertension. The success of these technologies has the potential to dramatically change conventional drug therapies used presently to treat the failing heart [6].

References:

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 [6] The authors acknowledge funding from the Distinguished Health Sciences Professorship of the University of South Carolina (D.J.D.) and by the National Science Foundation EPSCoR Program under NSF Award # OIA-1655740 (JDP).

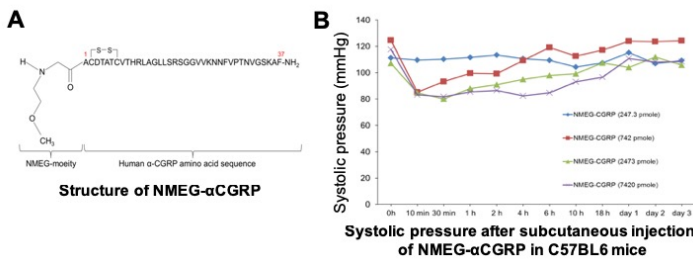


Figure 1. A) The structure of the NMEG- α CGRP peptide. B) The addition of NMEG- α CGRP to control animals shows a hypotensive property. A dose curve was achieved and normal bp was restored after 8hr of injection.

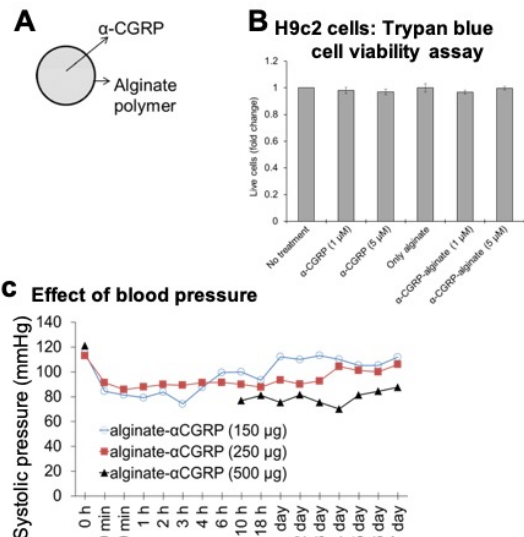


Figure 2. A) The structure of the alginate microcapsule containing α CGRP. B) Addition of α CGRP microcapsules had no toxic effects. C) The addition of NMEG- α CGRP to control animals shows a hypotensive property. A dose curve was achieved and normal bp was restored after 12hr of injection.