La Jolla, November 16th 2011

Dear Council members,

Hereby I would like to report on the outcome of the ESC First Contact Initiative Grant that was awarded to me in 2011. I would like to thank the members of the council for this grant. It has been pivotal for the next step in my career in basic science and cardiology. The grant was used to visit to the Lab of dr. Joan Heller Brown at the department of pharmacology of the University of California San Diego (UCSD). During my visit I gave a presentation on my previous work and had the opportunity to discuss the different projects with the individual team members and with several other scientists affiliated to the department. At the end of the visit I was offered a position as a postdoctoral fellow in her lab.

The ESC First Contact Initiative Grant has allowed met to build a constructive scientific relation with my future mentor before starting my post doc. It allowed me to chose a research project based on individual discussions with both the principal investigator and the colleagues with whom I now work on a daily basis. I believe that it has spearheaded my project and increased the likelihood of a success. Therefore, I would recommend it to everyone that aspires to advance his or her career in basic cardiovascular science. In the following paragraphs I will discuss the details of the project and present some preliminary results.

The role of Calcium-Calmodulin Kinase delta (CaMKIIδ) in heart failure has been a major focus of the Brown lab over the last decade. (Reviewed in ref 1) The lab has identified CaMKIIδ as a major signal transduction molecule involved in the pathogenesis of heart failure. CaMKIIδ is a serine–threonine kinase that is activated by calcium (Ca^{2+}) bound to calmodulin (CaM). CaMKIIδ is temporarily activated by the increases in cytoplasmatic Ca^{2+} that occur during every depolarization. However, sustained increases of Ca^{2+}/CaM or reactive oxygen species (ROS) transition CaMKIIδ into an autonomous active enzyme that is insensitive to Ca^{2+}/CaM concentrations and remains active throughout the cardiac cycle. CaMKIIδ targets several calcium-handling proteins in the sarcoplasmatic reticulum (SR), thereby stimulating SR calcium release and myocardial contractility. CaMKIIδ is also activated by increased calcium concentrations in the nucleus, where it induces the transcription of a hypertrophic gene program in cardiomyocytes. Although CaMKIIδ activation may initially improve cardiac performance, sustained activation of CaMKIIδ has the opposite effect. Indeed, overexpression of CaMKIIδ in mice causes heart failure while knockout of CaMKIIδ attenuates heart failure development.(2,3) The mechanism through which CaMKIIδ causes heart failure is unknown. Particularly, whether the changes in SR calcium release or the activation of a pathologic gene program are responsible is not clear.

Cytoplasmatic CAMKIIδ is predominantly activated during excitation, whereas nuclear CAMKIIδ is mainly activated by G protein coupled receptors, including the Gαq coupled receptors endothelin-1, angiotensin-II and norepinephrine.(4) Overexpression of Gαq in mice causes severe spontaneous heart failure without the extracardiac side effects of Gαq agonists such as hypertension.(5) Since Gαq causes heart failure and activates CAMKIIδ exclusively in the nucleus, it provides us with a model system to study whether receptor-induced nuclear CAMKIIδ activation may cause heart failure. We tested our hypothesis that Gαq-mediated nuclear activation of CAMKIIδ causes heart failure by crossing CAMKIIδ knockout mice with Gαq transgenic mice.

Deletion of CAMKIIδ attenuated the LV chamber dilation and dysfunction seen in Gαq TG mice (Fig 3A) and also diminished the occurrence of arrhythmias, cardiac fibrosis and apoptosis in mice overexpressing Gaq (not shown). Remarkably gene array studies revealed that the gene profiles are grossly similar i.e. the phenotypic rescue is not correlated with wholesale reversal of the pathological mRNA profile induced by Gq (Fig 3B). These data suggest that CaMKIIδ deletion has a powerfull ability to override genetically programmed pathological changes normally associated with HF through changes in a small number of genes or at a distinct step. Ongoing studies are directed at elucidating the genes responsible for the reversal of the phenotype.

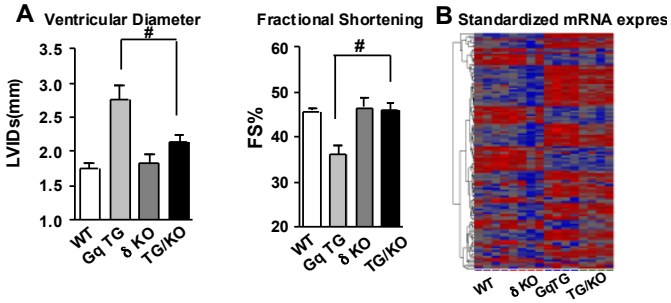

Fig 3. Heart failure development in Gαq TG mice is inhibited when CaMKIIδ is deleted. (**A**) CaMKIIδ deletion inhibits the LV chamber dilation and contractile dysfunctio induced by Gq overexpression (assessed by echocardiography; data are mean ± SEM of 3-6 determinations. #P < 0.05 versus Gαq-TG mice. (**B**) Heat map of mRNA transcrip for genes known to be regulated in the Gq TG mouse demonstrates surprisingly limited rescue by CaMKII deletion.

Yours sincerely,

B. Daan Westenbrink
Department of Pharmacology
University of California San Diego
9500 Gilman drive,
92093-0636
La Jolla, California

References:

1. Anderson ME, Heller Brown J, Bers D. CaMKII in myocardial hypertrophy and heart failure. JMCC 2011

2. Zhang T, Maier LS, Dalton ND, Miyamoto S, Ross Jr J, Bers DM, et al. The deltaC isoform of CaMKII is activated in cardiac hypertrophy and induces dilated cardiomyopathy and heart failure. Circ Res 2003;92(8):912–9.

3. Ling H, Zhang T, Pereira L, et al. Requirement for Ca2+/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. J Clin Invest 2009;119(5):1230–40.

4. Misra S, Gray C, Miyamoto S, Bers D, Brown JH. Location Matters: Clarifying the Concept of Nuclear and Cytosolic CaMKII Subtypes. Circ Res in press.

5. D'Angelo DD, Sakata Y, Lorenz JN, Boivin GP, Walsh RA, Liggett SB, Dorn GW 2nd. Transgenic Galphaq overexpression induces cardiac contractile failure in mice. Proc Natl Acad Sci U S A. 19978; 94:8121-6.