CRF 8G (Revised Sep 15)

RGC Reference: CUHK9/CRF/10
please insert ref. above

The Research Grants Council of Hong Kong
Collaborative Research Fund Group Research Projects
Completion Report

(for completed projects only)

Part A: The Project and Investigator(s)

1. Project Title

Schematic Identification of Predictors of Treatment Non-Responders in Patients with Systolic Heart Failure

收縮性心力衰竭治療無反應患者建立預測指標確認系統

2. Investigator(s) and Academic Department/Units Involved *(please highlight approved changes in the composition of the project team and quote the date when RGC granted approval of such changes)*

Research Team	Name/Post	Unit/Department/Institution	Average number of hours per week spent on this project in the current reporting period
Project Coordinator	Cheuk-Man YU / Professor of Medicine & Therapeutics;	Department of Medicine & Therapeutics/CUHK	4h
Co-Principal investigator(s)	Bryan P Yan / Associate Professor	Department of Medicine & Therapeutics/CUHK	2h
	Reinhard Renneberg / Professor of Chemistry	Hong Kong University of Science and Technology	2h
	Yat Yin Lam / Associate Professor	Department of Medicine & Therapeutics/CUHK	2h
	Hui-Yao Lan / Professor	LiHS, CUHK	2h
	John E Sanderson / Clinical Professor (Visiting)	Department of Medicine & Therapeutics, CUHK	2h
	Andrew Coats / Clinical Professor (Visiting)	Department of Medicine & Therapeutics, CUHK	2h
	Henry Krum / Professor of Medicine	Centre of Cardiovascular Research & Education in Therapeutics, Monash University, Australia	2h

	A Mark Richards /Professor in Medicine and Director	Department of Medicine, University of Otago, New Zealand	2h
Collaborators/ Others			

3. Project Duration

	Original	Revised	Date of RGC Approval *(must be quoted)*
Project Start Date	01-06-2011		
Project Completion Date	31-05-2014	30-11-2014	28-10-2014
Duration *(in month)*	36 months	42 months	28-10-2014
Deadline for Submission of Completion Report	30-06-2014	30-11-2015	28-10-2014

Part B: The Final Report

5. Project Objectives

5.1 Objectives as per original application

1. To establish the prevalence and clinical characteristics of CHF treatment non-responders through a prospective follow up study
2. To facilitate the identification of CHF treatment non-responders from responders by assessing the following potential features of non-responders:
   - (i) More significant myocardial dysfunction, both long- and short-axis, as well as reduced torsion (assessed by tissue Doppler imaging and speckle tracking echocardiography), as a result of higher scar burden,
   - (ii) More left ventricular adverse remodeling and unfavorable geometry (by 3D echo), as a result of higher scar burden (assessed by cardiac MRI),
   - (iii) More severe systolic and diastolic dyssynchrony (by echo)
   - (iv) More severe left ventricular diastolic dysfunction and higher filling pressures (by echo)
   - (v) More abnormality in biochemical biomarkers, in particular those related to fibrosis, inflammation and heart failure progression and myocyte damage
   - (vi) Up and/or down-regulation of selected molecular markers (microRNAs)
3. To develop an Assessment Model that predicts CHF treatment non-responders based on clinical, echocardiographic, biochemical and molecular biomarkers. New prognosticators will also be identified from this analysis
4. To investigate whether myocardial scar burden can be reflected by parameters developed from advanced echocardiographic tools

5.2 Revised objectives

Date of approval from the RGC: _____

Reasons for the change: _____

_____

1.
2.
3. ....

6. Research Outcome

6.1 Major findings and research outcome

(maximum 1 page; please make reference to Part C where necessary)

I. Clinical characteristics of Responders vs Non-responders

In our study, Non-Responders of HF treatment were defined as death, re-hospitalization for HF, and/or reduction of left ventricular end-systolic volume of <10% in 6 months. Based on these criteria, 63% of the HF patients were treatment Non-responders while 37% were Responders. It was observed that Non-responders were older (72±14 vs. 68±15 years, p<0.001), more likely to have diabetes mellitus (46% vs. 32%, p=0.002), more likely to have lower hemoglobin (12.0±2.4 vs. 12.5±2.7 years, p=0.03) at baseline when compared with Responders. Other baseline clinical characteristics were similar between the 2 groups

II. Biomarkers section

A panel of 23 different biomarkers related to inflammation, fibrosis or necrosis was assayed in 100 patients as a pilot study. Subsequently 5 biomarkers which have a high potential to identify heart failure treatment non-responders (NT-proBNP, Hs-TNT, MR pro ADM, GDF-15 and ST2 receptor) were selected for validation. Our results showed that 3 biomarkers including the NT-proBNP, Hs-TNT and GDF-15 were significantly higher in Non-responders than in Responders.

III. Echocardiographic section

According to the pre-defined criteria, all the patients were divided into responder (49%) and non-responder (51%). By using advanced echocardiographic imaging such as tissue Doppler imaging, it was found that there was a significantly impaired long-axis myocardial function during early diastole (septal mitral annular E', 4.4±2.1 vs 3.9±1.4 cm/s, P=0.013). In the multiple regression analysis, septal E' was independently predictive of HF treatment non-responder (HR: 0.837, 95% CI 0.73-0.96, P=0.011). We also used Automated Function Imaging (AFI), a novel algorithm of speckle-tracking echocardiography to assess global left ventricular peak systolic longitudinal strain. It was found that the value of global longitudinal strain by AFI was significantly lower in those non-responder to heart failure medical treatment.

IV. MicroRNA section

To establish the microRNA profiles in HF patients, we performed microarray assays (Affymetrix microRNA array v.2.0, USA) on RNAs from plasma samples. Taqman microRNA assays (Life technologies, USA) was employed as the quantitative real-time PCR measurement to validate the expression patterns of individual microRNAs in plasma samples from two independent groups of HF patients. Our studies demonstrated that circulating microRNAs are putative effective biomarkers of heart failure and of predicting treatment non-responders. We identified 7 microRNAs (miR-27b, miR-221, miR-222, miR-29b, miR-31, miR-140-3p, and miR-155) as the effective biomarkers for HF and they possess a high discriminatory ability to distinguish HF treatment non-responders from responders.

V. Predicting model for treatment non-responder

In order to create a risk model for predicting the treatment non-responder, all patients were randomly assigned as Derivation group and Validation Group with 1:1 ratio. In multivariate analysis, age ≥65 years [Odds ratio (OR) 2.15, 95% confidential interval (CI) 1.14-4.08, p=0.02], HsTNT ≥32.5 pg/ml (OR 2.32, 95% CI 1.28-4.19, p=0.005) and mitral annulus septal E' <8cm/s (OR 2.82, 95% CI 1.03-7.66, p=0.04) were found to be independent predictors of heart failure treatment non-responders. Based on the beta value and the constant in the multivariate analysis, we assigned each of the two variables a number of points that were proportional to its regression coefficient. They were: age<65y (0 point), age≥65y (5 points); Hs-TNT<32.5 pg/ml (0 point), Hs-TNT≥32.5 pg/ml (5.5 points); Mitral annulus septal E' ≥8 cm/s (0 point), Mitral annulus septal E'<8 cm/s (7 points). Area under ROC (AUC) in Derivation group was 0.70 (p<0.001). From the shoulder of the ROC, a cutoff value of 15 was identified with a sensitivity of 76%, specificity of 62%, positive predictive value of 80%, and negative predictive value of 57% and accuracy of 71%. In validation group, the area under the ROC was 0.67 (p=0.002) with a sensitivity of 58%, specificity of 70%, positive predictive value of 83%, negative predictive value of 41% and accuracy of 61%.

6.2 Potential for further development of the research and the proposed course of action *(maximum half a page)*

1. We can perform further study to identify the relationship between changes of levels of novel biomarkers in relation to heart failure treatment (such as GDF-15, ST-2 receptors) and the advanced echocardiographic parameters with respect to treatment response.
2. Recent research found that more than 50% of HF patients had relatively normal ejection fraction, the so called "heart failure with preserved ejection fraction" (HFPEF). We could try to find the prevalence and characteristics of treatment responders in HFPEF patients using the similar methods including conventional and advanced echocardiographic techniques, novel biomarkers and circulating microRNAs. We can also use these parameters to predict the long term outcome of HFPEF patients.
3. We can extend the concept of the current study to the area of device treatment for heart failure. Baseline and change of biomarkers and circulating microRNAs can be used to predict the long-term outcome of heart failure patients who received device therapy such as cardiac resynchronization therapy and cardiac contractility modulator.

6.3 Research collaboration achieved *(please give details on the achievement and its relevant impact)*

1. Under the collaboration with medical centers of Singapore, Australia and Mainland China, we enrolled more than 800 patients and found that treatment non-response were common in systolic HF patients. This was the first study which found the prevalence of treatment non-response in clinical practice, and explored the role of employing clinical characteristics, advanced echocardiographic technologies, novel biomarkers and relevant circulating microRNAs in predicting treatment non-response. This may help physicians to identify those patients who are likely to be non-responders of medical therapy and therefore should be candidates for consideration of more aggressive strategies or novel therapies.
2. During the study period, we collaborated with the Department of Chemistry, Hong Kong University of Science and Technology to explore the role of novel biomarkers to predict heart failure treatment response. In particular, Kyn/Trp and Neopterin were testified for the hypothesis.
3. We also collaborated with the reputed academic centers in cardiovascular medicine in Singapore and Australia and identified 3 biomarkers including the NT-pro BNP, Hs-TNT and GDF-15 which could predict the heart failure treatment non-response. With further validation studies, these biomarkers had a potential to be incorporated as part of the clinical management pathway in heart failure patients for their role in predict treatment non-responders and hence worse clinical outcome.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

We found that about 60% of the patients with systolic HF could be non-responders of standard anti-HF treatment in terms of poor clinical outcome or lack of left ventricular reverse remodeling. HF non-responders were found to have more severe impairment of left ventricular long-axis function. These include reduction of early diastolic velocity by tissue Doppler imaging and global strain by Automatic Function Imaging. In addition, the use of biomarkers, in particular NT-pro BNP, Hs-TNT and GDF-15, are helpful to predict treatment non-responders at medium-term follow-up. Furthermore, our study had identified 7 microRNAs (miR-27b, miR-221, miR-222, miR-29b, miR-31, miR-140-3p, and miR-155) as which possess a high discriminatory ability to distinguish HF treatment non-responders from responders. We also created a risk model using age, HsTNT and mitral septal E'. All these findings support our project hypothesis that treatment non-response is a common medical problem in HF patients, for which myocardial inflammation, necrosis and scarring may play important roles. Finally, we have demonstrated that novel biomarkers, advanced echocardiographic technologies and specific circulating microRNAs could be promising tools to identify patients who may respond sub-optimally to treatment, which prompt the development of more aggressive and novel treatment strategies in selected patients.

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Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of the publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) *(denote the corresponding author with an asterisk*)*	Title and Journal/Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Year of publication	Year of Acceptance (For paper accepted but not yet published)	Under Review	Under Preparation (optional)						
2015				Liu M, Fang F, Yu CM	Noncardiac comorbidities in heart failure with preserved ejection fraction - commonly ignored fact. Circ J. 2015;79(5):954-9	No	Yes	Yes	Yes
2014				Zhang Y, Huang XR, Wei LH, Chung AC, Yu CM, Lan HY	miR-29b as a therapeutic agent for angiotensin II-induced cardiac fibrosis by targeting TGF-β/Smad3 signaling. Mol Ther. 2014;22(5):974-85	No	Yes	Yes	Yes
2014				Luo XX, Fang F, Lee AP, Sun JP, Li S, Zhang ZH, Sanderson JE, Kwong JS, Zhang Q, Wang J, Yu CM.	What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol. 2014;172(1):132-7.	No	Yes	Yes	Yes
2014				Kwong JS, Yu CM.	Ultrafiltration for acute decompensated heart failure: a systematic review and meta-analysis	No	Yes	Yes	Yes

					of randomized controlled trials. Int J Cardiol 2014;172(2):395-402.				
2014				Fang F, Lee AP, Yu CM.	Left atrial function in heart failure with impaired and preserved ejection fraction. Curr Opin Cardiol.2014;29(5):430	No	Yes	Yes	Yes
2013				Yu CM, Hayes DL.	Cardiac resynchronization therapy: state of the art 2013. Eur Heart J. 2013;34(19):1396	No	Yes	Yes	Yes
2013				Wang S, Fang F, Liu M, Lam YY, Wang J, Shang Q, Sun JP, Sanderson JE, Yu CM.	Rapid bedside identification of high-risk population in heart failure with reduced ejection fraction by acoustic cardiography. Int J Cardiol. 2013;168(3):1881-6	No	Yes	Yes	Yes
2013				Fang F, Chan A, Lee AP, Sanderson JE, Kwong JS, Luo XX, Li S, Yu CM.	Variation in right ventricular volumes assessment by real-time three-dimensional echocardiography between dilated and normal right ventricle: comparison with cardiac magnetic resonance imaging. Int J Cardiol. 2013; 168(4):4391-3.	No	Yes	Yes	Yes
2013				Zhang Q, Chan YS, Liang YJ, Fang F, Lam YY, Chan CP, Lee AP, Chan KC, Wu EB, Yu CM.	Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure	Yes (2012)	Yes	Yes	Yes

					patients with different QRS durations. Int J Cardiol. 2013; 167(3):889-93.				
2013				Fang F, Chan JY, Lee AP, Sung SH, Luo XX, Jiang X, Kwong JS, Sanderson JE, Yu CM.	Improved coronary artery blood flow following the correction of systolic dyssynchrony with cardiac resynchronization therapy. Int J Cardiol. 2013; 167(5):2167-71	Yes (2012)	Yes	Yes	Yes
2013				Wei LH, Huang XR, Zhang Y, Li YQ, Chen HY, Yan BP, Yu CM, Lan HY.	Smad7 Inhibits Angiotensin II-induced Hypertensive Cardiac Remodeling. Cardiovasc Res. 2013; 99(4):665-73.	No	Yes	Yes	Yes
2013				Wang S, Lam YY, Liu M, Fang F, Wang J, Shang Q, Sun JP, Sanderson JE, Yu CM.	Acoustic cardiography helps to identify heart failure and its phenotypes. Int J Cardiol 2013; 167(3):681-6.	Yes (2012)	Yes	Yes	Yes
2012				Kwong JS, Sanderson JE, Yu CM.	Cardiac contractility modulation for heart failure: a meta-analysis of randomized controlled trials. Pacing Clin Electrophysiol. 2012;35(9):1111-8.	Yes (2012)	Yes	Yes	Yes
2012				Dong M, Liao JK, Fang F, Lee AP, Yan BP, Liu M, Yu CM.	Increased Rho kinase activity in congestive heart failure. Eur J Heart Fail. 2012 ;14(9):965-73.	Yes (2012)	Yes	Yes	Yes

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each conference abstract)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of RGC *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
05/2014/, Athens, Greece	Prevalence and Clinical Characteristics of Heart Failure Medical Treatment Non-responders.	European Society of Cardiology Heart Failure Congress 2014 (Poster Presentation)	No	Yes	Yes	Yes
5/2014/, Athens, Greece	Ultrafiltration in acute decompensated heart failure: not ready for prime time?	European Society of Cardiology Heart Failure Congress 2014 (Poster Presentation)	No	Yes	Yes	Yes
08/2014/ Barcelona, Spain	The third heart sound predicts mortality in heart failure with normal ejection fraction.	European Society of Cardiology Congress 2014 (Poster Presentation)	No	Yes	Yes	Yes
02/2013/ Hong Kong	Prevalence and Echocardiographic Predictors of Treatment Non-Responders in Patients with Systolic Heart Failure	CUHK-Mayo Clinic-Asia Cardiovascular Summit 2013 (Oral Presentation)	No	Yes	Yes	Yes
10/2013/ Hong Kong	Predicting Score System for Mid-term Responder of Cardiac Resynchronization Therapy in Patients Severe Heart Failure	Asian- Pacific Heart Rhythm Society Annual Meeting 2013. (Poster Presentation)	No	Yes	Yes	Yes
02/2013/ Hong Kong	Evaluation of global left ventricular systolic function in patients with heart failure using three-dimensional speckle-tracking echocardiography.	CUHK-Mayo Clinic-Asia Cardiovascular Summit 2013 (Poster Presentation)	No	Yes	Yes	Yes
11/2013/ Istanbul, Turkey	Feasibility of assessing left ventricular function in hypertensive heart failure patients using endocardial area strain: a novel index derived from three-dimensional speckle-tracking echocardiography	Scientific Annual meeting of European Society of Echocardiography (Euro Echo) 2013 (Poster Presentation)	No	Yes	Yes	Yes
08/2013/ Amsterdam, Netherlands	Ultrafiltration for acute decompensated heart failure: a systematic review and meta-analysis of randomized controlled trials.	European Society of Cardiology (ESC) Congress 2013 (Poster Presentation)	No	Yes	Yes	Yes

11/2013/ Dallas, USA	Mode of Death in Patients with Heart Failure and Preserved Ejection Fraction.	Scientific Annual meeting of American heart Association (AHA) 2013 (Poster Presentation)	No	Yes	Yes	Yes
08/2013/ Amsterdam, Netherlands	Predictive Value of Novel Biomarkers for Response to Medical Treatment in Systolic Heart Failure.	European Society of Cardiology (ESC) Congress 2013 (Poster Presentation)	No	Yes	Yes	Yes
08/2013/ Amsterdam, Netherlands	Circulating microRNAs as markers for prediction of heart failure medical treatment outcome.	European Society of Cardiology (ESC) Congress 2013 (Poster Presentation)	No	Yes	Yes	Yes
12/2012/ Athens, Greece	Left Ventricular Twist Mechanics in Heart Failure Patients: Insights from Three-Dimensional Speckle Tracking Echocardiography	Scientific Annual meeting of European Society of Echocardiography (Poster Presentation, Euroecho 2012)	No	Yes	Yes	Yes
12/2012/ Athens. Greece	Variation in Right Ventricular Volumes Assessment by Real-Time Three-dimensional Echocardiography between Dilated and Normal Right Ventricle: Comparison with Cardiac Magnetic Resonance Imaging	Scientific Annual meeting of European Society of Echocardiography (Euroecho) 2012 Poster Presentation,	No	Yes	Yes	Yes
12/2012/ Athens. Greece	Relationship between acoustic cardiographic and echocardiographic evaluation of left ventricular function in heart failure.	Scientific Annual meeting of European Society of Echocardiography (Euroecho 2012) Poster Presentation	No	Yes	Yes	Yes
11/2012/ Los Angles, USA	Smad7 Enhances Myocardial Remodeling Induced by Angiotensin II.	Scientific Annual meeting of American heart Association (AHA 2012) Oral Presentation	No	Yes	Yes	Yes
11/2012/ Los Angles, USA	Quality of Life in Elderly Patients with Heart Failure and Preserved Ejection Fraction	Scientific Annual meeting of American heart Association (AHA 2012) Poster Presentation	No	Yes	Yes	Yes
11/2012/ Los Angles, USA	Improvement of Left Ventricular Mechanics and its Relationship with Reverse Remodeling in Patients Treated by Cardiac Contractility Modulation	Scientific Annual meeting of American heart Association (AHA 2012) Poster Presentation	No	Yes	Yes	Yes

07/2012 Munich, Germany	Acoustic cardiography helps to identify heart failure and its phenotypes	European Society of Cardiology Congress 2012 (Poster Presentation)	No	Yes	Yes	Yes
07/2012 Munich, Germany	Risk stratification for 1 year mortality in patients with heart failure and normal ejection fraction.	European Society of Cardiology Congress 2012 (Oral Presentation)	No	Yes	Yes	Yes
07/2012 Munich, Germany	Assessment of left ventricular myocardial deformation and mechanical dyssynchrony in patients with heart failure: insights from three-dimensional wall motion analysis	European Society of Cardiology Congress 2012 (Poster Presentation)	No	Yes	Yes	Yes
07/2012 Singapore	Cardiac contractility modulation for heart failure: a meta-analysis of randomized controlled trials	ASEAN Federation of Cardiology Congress (Poster Presentation)	No	Yes	Yes	Yes
02/2012/ Hong Kong	Feasibility of assessing left ventricular function in heart failure using global area strain: A novel index derived from three-dimensional speckle-tracking echocardiography.	International Congress of Cardiology 2012 (Poster Presentation)	No	Yes	Yes	Yes
02/2012/ Hong Kong	Noninvasive evaluation of heart failure with reduced ejection fraction by acoustic cardiography	International Congress of Cardiology 2012 (Poster Presentation)	No	Yes	Yes	Yes
02/2012/ Hong Kong	Acoustic cardiography facilitates identifying heart failure with normal ejection fraction.	International Congress of Cardiology 2012 (Poster Presentation)	No	Yes	Yes	Yes
02/2012/ Hong Kong	miR-29 Inhibits Angiotensin II-induced Cardiac Fibrosis.	International Congress of Cardiology 2012 (Poster Presentation)	No	Yes	Yes	Yes
02/2012/ Hong Kong	Smad7 as a Novel Therapeutic Agent for Hypertensive Cardiac Disease.	International Congress of Cardiology 2012 (Poster Presentation)	No	Yes	Yes	Yes

10. ***Student(s) trained*** (please attach a copy of the title page of the thesis)

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation

11. **Other impact** *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

N/A

Project Coordinator

Contact Information:

Tel: 2632 3717, Email: cmyu@cuhk.edu.hk