

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
磯部光章	Yamamoto T, Suganami T, Kiso-Narita M, Scherle PA, Kamei Y, Isobe M, Higashiyama S, Ogawa Y	Insulin-induced Ectodomain Shedding of Heparin-binding Epidermal Growth Factor-like Growth Factor in Adipocytes	In Vitro.Obsity			in press
	Ogawa M, Suzuki J, Yamaguchi Y, Muto S, Itai A, Hirata Y, Isobe M, Nagai R	The effects of pharmacological plasminogen activator inhibitor-1 inhibition in acute and chronic rejection in murine cardiac allografts.	Transplantation	91	21-26	2011
	Konishi M, Haraguchi G, Ishihara T, Ohgashi H, Saito K, Nakano Y, Isobe M	Adiponectin protects doxorubicin-induced cardiomyopathy by anti-apoptotic effects through AMPK upregulation in mice.	Cardiovasc Res			in press
	Maejima Y, Nobori K, Ono Y, Adachi S, Suzuki J, Hirao K, Isobe M, Ito H	Synergistic Effect of Combined HMG-CoA Reductase Inhibitor (Statin) and Angiotensin-II Receptor Blocker Therapy in Patients with Chronic Heart Failure - The HF-COSTAR Trial-	Circ J			in press
	Ngoc PB, Suzuki J, Ogawa M, Hishikari K, Takayama K, Hirata Y, Nagai R, Isobe M	The anti-inflammatory mechanism of prostaglandin E2 receptor 4 activation in rat experimental autoimmune myocarditis.	J Cardiovasc Pharm			in press
	Maejima Y, Okada H, Haraguchi G, Onai M, Kosuge H, Suzuki J, Hirao K, Isobe M	Telmisartan, a Unique ARB, Improves Left Ventricular Remodeling of Infarcted Heart by Activating PPAR gamma.	Lab Invest			in press
	稲村幸洋、大友建一郎、金地嘉久、木田夏子、高木崇光、鈴木麻美、栗原顕、小野裕一、鈴木紅、清水茂雄、川上正人、磯部光章	マラソン中の心臓突然死の臨床的特徴と対策	適応医学	14	33-39	2011
	手塚大介、鈴木淳一、原口剛、川良徳弘、松浦雅人、田村典子、稲垣裕、蜂谷仁、平尾見三、磯部光章	Continuous ositive airway pressureを導入した連続61例における脱落例の臨床的背景	適応医学	14	68-73	2011
鈴木淳一、小川真仁、田村典子、本多和樹、前村浩二、平田恭信、永井良三、磯部光章	食塩負荷Dahlラットにおける増悪した睡眠-覚醒日内リズムに対するベータ遮断剤の改善効果	適応医学	14	74-80	2011	

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
後藤雄一	Mtsushima Y, Goto Y, Kagni L	Mitochondrial Lon protease regulates mitochondrial DNA copy number and transcription by selective degeneration of mitochondrial transcription factor A (TFAM)	Proc Natl Acad Sci USA	107	18410-18415	2010
	Mimaki M, Hatakeyama H, Komaki H, Yokoyama M, Arai H, Kirino Y, Suzuki T, Nishino I, Nonaka I, Goto Y.	Reversible infantile respiratory chain deficiency: a clinical and molecular study.	Ann Neurol	68	845-854	2010
山岸正和	Funada A et al.	Impact of renin-angiotensin system polymorphisms on development of systolic dysfunction in hypertrophic cardiomyopathy. Evidence from a study of genotyped patients.	Circ J	74	2674-80	2010
	Funada A et al.	Heterogeneity of clinical manifestation of hypertrophic cardiomyopathy caused by deletion of lysine 183 in cardiac troponin I gene.	Int Heart J	51	214-7	2010
木村剛	Kato T, Niizuma S, Inuzuka Y, Kawashima T, Okuda J, Tamaki Y, Iwanaga Y, Narazaki M, Matsuda T, Soga T, Kita T, Kimura T, Shioi T.	Analysis of Metabolic Remodeling in Compensated Left Ventricular Hypertrophy and Heart Failure.	Circ Heart Fail.	3	420-30	2010
小室一成	Toko H, Takahashi H, Kayama Y, Oka T, Minamino T, Okada S, Morimoto S, Zhan DY, Terasaki F, Anderson ME, Inoue M, Yao A, Nagai R, Kitaura Y, Sasaguri T, Komuro I.	Ca ²⁺ /calmodulin-dependent kinase II δ causes heart failure by accumulation of p53 in dilated cardiomyopathy.	Circulation	122(9)	891-9	2010
	Shimizu I, Minamino T, Toko H, Okada S, Ikeda H, Yasuda N, Tateno K, Moriya J, Yokoyama M, Nojima A, Koh GY, Akazawa H, Shiojima I, Kahn CR, Abel ED, Komuro I.	Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents.	J Clin Invest	120(5)	1506-14	2010
	Naito AT, Okada S, Minamino T, Iwanaga K, Liu ML, Sumida T, Nomura S, Sahara N, Mizoroki T, Takashima A, Akazawa H, Nagai T, Shiojima I, Komuro I.	Promotion of CHIP-mediated p53 degradation protects the heart from ischemic injury.	Circ Res	106(11)	1692-702	2010
	Ueda K, Takano H, Niitsuma Y, Hasegawa H, Uchiyama R, Oka T, Miyazaki M, Nakaya H, Komuro I.	Sonic hedgehog is a critical mediator of erythropoietin-induced cardiac protection in mice.	J Clin Invest	120(6)	2016-29	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
中谷武嗣	築瀬正伸、中谷武嗣	心臓移植交代関連拒絶反応の診断と治療	心臓	42	20-25	2010
	土井洋平、吉原史樹、中村敏子、小川浩司、井口公平、植田初江、屋宜宣仁、堀尾武史、岩嶋義雄、林輝行、中谷武嗣、大塚頼隆、河野雄平	拡張型心筋症による心原性ショック、多臓器不全に対し急性血液浄化法を施行し補助人工心臓装着に至った1例	透析会誌	43	847-851	2010
齋藤能彦	Uesugi Y, Kawata H, Jo J, Saito Y, Tabata Y	An ultrasound-responsive nano delivery system of tissue-type plasminogen activator for thrombolytic therapy.	J Control Release.	15	269-77	2011
	Onoue K, Zaima N, Sugiura Y, Isojima T, Okayama S, Horii M, Akai Y, Uemura S, Takemura G, Sakuraba H, Sakaguchi Y, Setou M, Saito Y	Imaging Mass Spectrometry to Accurately Diagnose Fabry's Disease.	Circ J.	24	221-3	2010
	Nakatani K, Yoshimoto S, Iwano M, Asai O, Samejima K, Sakan H, Terada M, Hasegawa H, Nose M, Saito Y	Fractalkine expression and CD16+ monocyte accumulation in glomerular lesions: association with their severity and diversity in lupus models.	Am J Physiol Renal Physiol.	299	F207-16	2010
	Harada K, Miyamoto Y, Morisaki H, Ohta N, Yamanaka I, Kokubo Y, Makino H, Harada-Shiba M, Okayama A, Tomoike H, Okamura T, Saito Y, Yoshimasa Y, Morisaki T	A novel Thr56Met mutation of the autosomal recessive hypercholesterolemia gene associated with hypercholesterolemia.	J Atheroscler Thromb.	26	131-40	2010
松崎益徳	Hitoshi Uchinomi, Masafumi Yano, Takeshi Suetomi, Makoto Ono, Xiaojuan Xu, Hiroki Tateishi, Tetsuro Oda, Shinichi Okuda, Masahiro Doi, Shigeki Kobayashi, Takeshi Yamamoto, Yasuhiro Ikeda, Tomoko Ohkusa, Noriaki Ikemoto, Masunori Matsuzaki	「Catecholaminergic polymorphic ventricular tachycardia is caused by mutation-linked defective conformational regulation of the ryanodine receptor」	Circ Res	106(8)	1413-1424	2010
	Xiaojuan Xu, Masafumi Yano, Hitoshi Uchinomi, Akihiro Hino, Takeshi Suetomi, Makoto Ono, Hiroki Tateishi, Tetsuro Oda, Shinichi Okuda, Masahiro Doi, Shigeki Kobayashi, Takeshi Yamamoto, Yasuhiro Ikeda, Noriaki Ikemoto, Masunori Matsuzaki	「Defective calmodulin binding to the cardiac ryanodine receptor plays a key role in CPVT-associated channel dysfunction」	Biochem Biophys Res Commun	394(3)	660-666	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
松 崎 益 徳	Yoshio Nose, Kazuya Murata, Yasuaki Wada, Takeo Tanaka, Yasuhiro Fukagawa, Hiroko Yoshino, Takehisa Susa, Chikage Kihara, Masunori Matsuzaki	「The Impact of Intermittent Pneumatic Compression Devices on Deep Venous Flow Velocity in Patients with Congestive Heart Failure」	J Cardiol	55(3)	384-390	2010
	Masaki Shibuya, Toshiro Miura, Yasuhiro Fukagawa, Shintaro Akashi, Takamasa Oda, Shuji Kawamura, Yasuhiro Ikeda, Masunori Matsuzaki	「Tongue Muscle-Derived Stem Cells Express Connexin 43 and Improve Cardiac Remodeling and Survival After Myocardial Infarction in Mice」	Circ J	74(6)	1219-1226	2010
	Miyuki Ando, Takeshi Yamamoto, Akihiro Hino, Takashi Sato, Yasuma Nakamura, Masunori Matsuzaki	「Norepinephrine spillover during exercise as a novel parameter to evaluate the severity of heart failure」	J Nucl Cardiol	17(5)	868-873	2010
	Ryo Hashimoto, Seiji Umamoto, Fengling Guo, Kyoko Umeji, Shinichi Itoh, Hiroko Kishi, Sei Kobayashi, Masunori Matsuzaki	「Nifedipine Activates PPAR γ and Exerts an Antioxidative Action Through Cu/ZnSOD Independent of Blood-pressure Lowering in SHRSP」	J Atheroscler Thromb	17(8)	785-795	2010
	Takafumi Hiro, Takeshi Kimura, Takeshi Morimoto, Katsumi Miyauchi, Yoshihisa Nakagawa, Masakazu Yamagishi, Yukio Ozaki, Kazuo Kimura, Satoshi Saito, Tetsu Yamaguchi, Hiroyuki Daida, Masunori Matsuzaki	「Diabetes Mellitus Is a Major Negative Determinant of Coronary Plaque Regression During Statim Therapy in Patients With Acute Coronary Syndrome -Serial Intravascular Ultrasound Observations From the JAPAN Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome Trial (the JAPAN-ACS Trial)-」	Circ J	74(6)	1165-1174	2010
	Naoki Sugi, Akihiko Shimizu, Takeshi Ueyama, Yasuhiro Yoshiga, Masahiro Doi, Toshihide Ohmiya, Makoto Ono, Masa-aki Yoshida, Masunori Matsuzaki	「What Variables were Associated with the Inducibility of Ventricular Fibrillation During Electrophysiologic Stimulation Test in Patients without Apparent Organic Heart Disease?」	J Cardiol	56(1)	35-43	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
松崎益徳	Yuichi Ishikawa, Mitsuhiro Yokoyama, Yasushi Saito, Masunori Matsuzaki, Hideki Origasa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya for the JELIS Investigators, Japan	「Preventive Effects of Eicosapentaenoic Acid on Colony Artery Disease in Patients With Peripheral Artery Disease」	Circ J	74(7)	1451-1457	2010
	Hidekazu Aoyama*, Yasuhiro Ikeda*, Yousuke Miyazaki, Koichi Yoshimura, Shizuka Nishino, Takeshi Yamamoto, Masafumi Yano, Makoto Inui, Hiroki Aoki, Masunori Matsuzaki(*co-first author)	「Isoform-Specific Roles of Protein Phosphatase 1 Catalytic Subunits in Sarcoplasmic Reticulum- Mediated Ca ²⁺ Cycling」	Cardiovas Res	89(1)	79-88	2010
	Hitomi Ono, Hiroshi Nakamura, Masunori Matsuzaki	「A NADH Dehydrogenase Ubiquinone Flavoprotein is Decreased in Patients with Dilated Cardiomyopathy」	Intern Med	49(19)	2039-2042	2010
	Yasuhiro Yoshiga, Akihiko Shimizu, Shinsuke Suzuki, Naoki Sugi, Toshihide Omiya, Makoto Ono, Masaaki Yoshida and Masunori Matsuzaki	「Catheter Ablation for Electrical Storm as Polymorphic Ventricular Tachycardia in a Case with Ischemic Cardiomyopathy after Coronary Artery Bypass Graft」	J Arrhythmia	26(2)	140-145	2010
	Makoto Ono, Masafumi Yano, Akihiro Hino, Takeshi Suetomi, Xiaojuan Xu, Takehisa Susa, Hitoshi Uchinoumi, Hiroki Tateishi, Tetsuro Oda, Shinichi Okuda, Masahiro Doi, Shigeki Kobayashi, Takeshi Yamamoto, Noritaka Koseki, Hiroyuki Kyushiki, Noriaki Ikemoto, Masunori Matsuzaki	「Dissociation of calmodulin from cardiac ryanodine receptor causes aberrant Ca ²⁺ release in heart failure」	Cardiovasc Res	87(4)	609-617	2010
	Shigeki Kobayashi, Masafumi Yano, Hitoshi Uchinoumi, Takeshi Suetomi, Takehisa Susa, Makoto Ono, Xiaojuan Xu, Hiroki Tateishi, Tetsuro Oda, Shinichi Okuda, Masahiro Doi, Takeshi Yamamoto, Masunori Matsuzaki	「Dantrolene, a Therapeutic Agent for Malignant Hyperthermia, Inhibits Catecholaminergic Polymorphic Ventricular Tachycardia in a RyR2R2474S/+ Knock-In Mouse Model」	Circ J	74(12)	2579-2584	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
松崎益徳	Shigeki Kobayashi, Takehisa Susa, Takeo Tanaka, Yasuaki Wada, Shinichi Okuda, Masahiro Doi, Tomoko Nao, Yasuhiro Yoshiga, Jutaro Yamada, Takayuki Okamura, Takeshi Ueyama, Shuji Kawamura, Masafumi Yano, Masunori Matsuzaki	「Urinary 8-hydroxy-2'-deoxyguanosine reflects symptomatic status and severity of systolic dysfunction in patients with chronic heart failure」	Euro J Heart Fail	13(2)	29-36	2011
今泉勉	Koiwaya H, Sasaki K, Ueno T, Yokoyama S, Toyama Y, Ohtsuka M, Nakayoshi T, Mitsutake Y, Imaizumi T	Augmented neovascularization with magnetized endothelial progenitor cells in rats with hind-limb ischemia.	J Mol Cell Cardiol		in press	2011
	Mori T, Kai H, Kajimoto H, Koga M, Kudo H, Takayama N, Yasuoka S, Anegawa T, Kai M, Imaizumi T	Enhanced cardiac inflammation and fibrosis in ovariectomized hypertensive rats -a possible mechanism of diastolic dysfunction in postmenopausal women-	Hypertens Res		in press	2011
	Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, Imai Y, Kikuchi K, Ito S, Eto T, Kimura G, Imaizumi T, Takishita S, Ueshima H, for the Valsartan in Elderly Isolated Systolic Hypertension Study Group	Target blood pressure for treatment of isolated systolic hypertension in the elderly. - Valsartan in elderly isolated systolic hypertension study –	Hypertension		in press	2011
	Nagamoto Y, Inage T, Yoshida T, Takeuchi T, Gondo T, Fukuda Y, Takii E, Murotani K, Imaizumi T	Atrioventricular nodal ablation vs. antiarrhythmic drugs after permanent pacemaker implantation for bradycardia-tachycardia syndrome.	Heart and Vessels		in press	2011
	Fukuda Y, Yoshida T, Inage T, Takeuchi T, Gondo T, Takii E, Imaizumi T	Long-term results of maze procedure on left ventricular function for persistent atrial fibrillation associated with mitral valve disease.	Heart and Vessels		in press	2011
	Fukami A, Yamagishi S, Adachi H, Matsui T, Yoshikawa K, Ogata K, Kasahara A, Tsukagawa E, Yokoi K, Imaizumi T	High white blood cell counts and low estimated glomerular filtration rate (eGFR) are independently associated with serum levels of monocyte chemoattractant protein-1 (MCP-1) in a general population.	Clin Cardiol		in press	2011
	Ueda S, Yamagishi S, Matsui T, Noda Y, Ueda S-I, Jinnouchi Y, Sasaki K, Takeuchi M, Imaizumi T	Serum levels of advanced glycation end products (AGEs) are inversely associated with number and migratory activity of circulating endothelial progenitor cells in apparently healthy subjects.	Cardiovasc Ther		in press	2011

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
今泉勉	Tahara N, Yamagishi S, Matsui T, Takeuchi M, Nitta Y, Kodama N, Mizoguchi M, Imaizumi T	Serum levels of advanced glycation end products (AGEs) are independent correlates of insulin resistance in nondiabetic subjects.	Cardiovasc Ther		in press	2011
	Nanjo Y, Adachi H, Hirai Y, Enomoto M, Fukami A, Otsuka M, Yoshikawa K, Yokoi K, Ogata K, Tsukagawa E, Kasahara A, Murayama K, Yasukawa H, Kojima M, Imaizumi T	Factors associated with plasma ghrelin level in Japanese general population.	Clin Endocrinol	74(4)	453-458	2011.4
	Sugi Y, Yasukawa H, Kai H, Fukui D, Futamata N, Mawatari K, Oba T, Nagata N, Kyougoku S, Koga M, Imaizumi T	Reduction and activation of circulating dendritic cells in patients with decompensated heart failure.	Int J Cardiol	147(2)	258-264	2011.3
	Takayama N, Kai H, Kudo H, Yasuoka S, Mori T, Anegawa T, Koga M, Kajimoto H, Hirooka Y, Imaizumi T	Simvastatin prevents large blood pressure variability induced aggravation of cardiac hypertrophy in hypertensive rats by inhibiting RhoA/Ras-ERK pathways.	Hypertens Res	34(3)	341-347	2011.3
	Ueda S-I, Yamagishi S, Matsui T, Jinnouchi Y, Imaizumi T	Administration of pigment epithelium-derived factor inhibits left ventricular remodeling and improves cardiac function in rats with acute myocardial infarction.	Am J Pathol	178(2)	591-598	2011.2
	Katsuki Y, Sasaki K, Toyama Y, Ohtsuka M, Koiwaya H, Nakayoshi T, Imaizumi T	Early outgrowth EPCs generation is reduced in patients with Buerger's disease.	Clin Res Cardiol	100	21-27	2011.1
	Umei H, Yamagishi S, Imaizumi T	Positive association of serum levels of pigment epithelium-derived factor with high-sensitivity C-reactive protein in apparently healthy unmedicated subjects.	J Int Med Res	38(2)	443-448	2010
	Arima K, Yamagishi S, Matsui T, Saito Y, Katsuki Y, Sasaki K, Katsuda Y, Kai H, Imaizumi T	Inhibition of pigment epithelium-derived factor (PEDF) augments vascular endothelial growth factor (VEGF)-induced recovery of limb perfusion after ischemia in klotho mouse.	Letters in Drug Design & Discovery	7(7)	541-545	2010
	Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H, Baba K, Ishibashi M, Hayabuchi N, Narula J, Imaizumi T	Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis.	JACC: Cardiovasc Imaging	3(12)	1219-1228	2010.1

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
今泉勉	Kumagai S, Adachi H, Jacobs Jr. DR, Hirai Y, Enomoto M, Fukami A, Otsuka M, Nanjo Y, Esaki E, Kumagai E, Yoshikawa K, Yokoi K, Ogata K, Tsukagawa E, Kasahara A, Murayama K, Imaizumi T	High level of plasma endothelin-1 predicts development of hypertension in normotensive subjects.	Am J Hypertens	23(10)	1103-1107	2010.1
	Noda Y, Yamagishi S, Matsui T, Ueda S, Ueda S-I, Jinnouchi Y, Hirai Y, Imaizumi T	The p66shc gene expression in peripheral blood monocytes is increased in patients with coronary artery disease.	Clin Cardiol	33(9)	548-552	2010.9
	Nakamura K, Yamagishi S, Adachi H, Matsui T, Kurita Y, Imaizumi T	Serum levels of pigment epithelium-derived factor (PEDF) are an independent determinant of insulin resistance in patients with essential hypertension.	Int J Cardiol	143(1)	96-98	2010.8
	Arima K, Katsuda Y, Takeshita Y, Saito Y, Toyama Y, Katsuki Y, Ootsuka M, Koiwaya H, Sasaki K, Kai H, Imaizumi T	Autologous transplantation of bone marrow mononuclear cells improved ischemic peripheral neuropathy in humans.	J Am Coll Cardiol	56(3)	238-239	2010.7
	Takemiya K, Kai H, Yasukawa H, Tahara N, Kato S, Imaizumi T	Mesenchymal stem cell-based prostacyclin synthase gene therapy for pulmonary hypertension in rats.	Basic Res Cardiol	105(3)	409-417	2010.5
鄭忠和	Miyata M, Tei C	Waon therapy for cardiovascular disease: innovative therapy for the 21st century	Circ J	74	617-621	2010
	Shinsato T, Miyata M, Kubozono T, Ikeda Y, Fujita S, Kuwahata S, Akasaki Y, Hamasaki S, Fujiwara H, Tei C	Waon therapy mobilizes CD34+ cells and improves peripheral arterial disease	J Cardiol	56	361-366	2010
	Kono M, Kisanuki A, Ueya N, Kubota K, Kuwahara E, Takasaki K, Yuasa T, Mizukami N, Miyata M, Tei C	Left ventricular global systolic dysfunction has a significant role in the development of diastolic heart failure in patients with systemic hypertension	Hypertens Res	33	1167-1173	2010
	Kuwahata S, Miyata M, Fujita S, Kubozono T, Shinsato T, Ikeda Y, Hamasaki S, Kuwaki T, Tei C	Improvement of autonomic nervous activity by Waon therapy in patients with chronic heart failure	J Cardiol	57	100-106	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
鄭 忠 和	Higuchi K, Yoshimitsu M, Fan X, Guo X, Rasiaah VI, Yen J, Tei C, Takenaka T, Medin JA	Alpha-galactosidase A-Tat fusion enhances storage reduction in hearts and kidneys of Fabry mice	Mol Med	16	216-221	2010
	Fujita S, Ikeda Y, Miyata M, Shinsato T, Kubozono T, Kuwahata S, Hamada N, Miyauchi T, Yamaguchi T, Torii H, Hamasaki S, Tei C	Effect of Waon therapy on oxidative stress in chronic heart failure	Circ J.	75	348-56	2011
豊 岡 照 彦	石川 憲彦, 豊岡 照彦	うつ病の合併は慢性腎臓病の予後に関連する か?	毎日メカニカル	12	432-433	2010
竹 石 恭 知	Kaneshiro T, Saitoh S, Machii H, Yamaguchi O, Ishibashi T, Maruyama Y, Takeishi Y	Metabolic regulation of coronary vascular tone: role of hydrogen peroxide, purinergic components, and angiotensin	European Journal of Pharmacology	645 (1- 3)	127-134	2010
	Sasaki T, Takeishi Y, Suzuki S, Niizeki T, Kitahara T, Katoh S, Ishino M, Shishido T, Kubota I	High serum level of neopterin is a risk factor of patients with heart failure	International Journal of Cardiology	145 (2)	318	2010
	Ogawa K, Ikeda K, Furukawa M, Shirado K, Mashimo Y, Takahashi H, Matsumoto H, Kimura S, Nakamura A, Ohkawara H, Hashimoto Y, Asahi K, Noji H, Ohto H, Takeishi Y	A long-term remission of renal amyloidosis with nephrotic syndrome after autologous peripheral blood stem-cell transplantation	Fukushima Journal of Medical Science	56 (2)	151-156	2010
	Yoshihisa A, Owada T, Hoshino Y, Miyata M, Misaka T, Sato T, Suzuki S, Sakamoto N, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S, Ishibashi T, Takeishi Y	Flow-mediated dilatation identifies impaired endothelial function in patients with sleep apnea syndrome	Fukushima Journal of Medical Science	56 (2)	115-120	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
竹石恭知	Ogawa K, Noji H, Furukawa M, Shirado K, Mashimo Y, Takahashi H, Matsumoto H, Kimura S, Nakamura A, Ohkawara H, Ikeda K, Ohto H, Takeishi Y	Hematopoietic stem cell transplantation in the department of hematology, Fukushima Medical University	Fukushima Journal of Medical Science	56 (2)	107-114	2010
	Otake A, Saitoh S, Takeishi Y	Hydrogen peroxide generated from cardiac myocytes impacts metabolic dilation in coronary arterioles	International Heart Journal	51 (2)	125-128	2010
	Tase C, Ohno Y, Hasegawa A, Tsukada Y, Shimada J, Ikegami Y, Sakamoto N, Takeishi Y	Survival of a refractory ventricular fibrillation by cooperative treatments	Fukushima Journal of Medical Science	56 (2)	139-143	2010
	Ohkawara H, Ishibashi T, Saitoh S, Inoue N, Sugimoto K, Kamioka M, Uekita H, Kaneshiro T, Ando K, Takuwa Y, Maruyama Y, Takeishi Y	Preventive effects of pravastatin on thrombin-triggered vascular responses via Akt/eNOS and RhoA/Rac1 pathways in vivo	Cardiovascular Research	88 (3)	492-501	2010
	Nakamura S, Yuhei K, Hase H, Hatta T, Nishimura S, Moroi M, Nakagawa S, Kasai T, Kusuoka H, Takeishi Y, Nakajima K, Momose M, Takehana K, Nanasato M, Yoda S, Nishina H, Matsumoto N, Nishimura T	Prognostic study of cardiac and renal events in Japanese patients with chronic kidney disease and cardiovascular risk using myocardial perfusion SPECT: J-ACCESS 3 study design	Therapeutic Apheresis and Dialysis	14 (4)	379-385	2010
	Takano M, Watanabe M, Otake H, Kobayashi A, Oikawa M, Machii H, Misaka T, Watanabe T, Takeishi Y	Tricuspid valvular dysplasia and its differentiation from Ebstein's anomaly	Journal of Echocardiography	8 (4)	137-139	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
竹石恭知	Kitahara T, Shishido T, Suzuki S, Katoh S, Sasaki T, Ishino M, Nitobe J, Miyamoto T, Miyashita T, Watanabe T, Takeishi Y, Kubota I	Serum midkine as a predictor of cardiac events in patients with chronic heart failure	Journal of Cardiac Failure	16 (4)	308-313	2010
	Shichishima T, Ikeda K, Takahashi N, Kameoka J, Tajima K, Murai K, Tamai Y, Nakamura A, Akutsu K, Noji H, Okamoto M, Kimura H, Harigae H, Oyamada T, Kamesaki T, Takeishi Y, Sawada K	Low concentration of serum haptoglobin has impact on understanding complex pathophysiology in patients with acquired bone marrow failure syndromes	International Journal of Hematology	91 (4)	602-610	2010
	Ishibashi T, Kawaguchi M, Sugimoto K, Uekita H, Sakamoto N, Yokoyama K, Maruyama Y, Takeishi Y	Advanced glycation end product-mediated matrix metallo-proteinase-9 and apoptosis via renin-angiotensin system in type 2 diabetes	Journal of Atherosclerosis and Thrombosis	17 (6)	578-589	2010
	Kamioka M, Ishibashi T, Sugimoto K, Uekita H, Nagai R, Sakamoto N, Ando K, Ohkawara H, Teramoto T, Maruyama Y, Takeishi Y	Blockade of renin-angiotensin system attenuates advanced glycation end products-mediated signaling pathways	Journal of Atherosclerosis and Thrombosis	17 (6)	590-600	2010
	Bilim O, Takeishi Y, Kitahara T, Ishino M, Sasaki T, Suzuki S, Shishido T, Kubota I	Serum YKL-40 predicts adverse clinical outcomes in patients with chronic heart failure	Journal of Cardiac Failure	16 (11)	873-879	2010
	Machii H, Saitoh S, Kaneshiro T, Takeishi Y	Aging impairs myocardium-induced dilation in coronary arterioles: role of hydrogen peroxide and angiotensin	Mechanisms of Ageing and Development	131 (11-12)	710-717	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
竹石恭知	Takeishi Y	The nitric oxide synthase family and left ventricular diastolic function	Circulation Journal	74 (12)	2556-2557	2010
	宮田真希子, 中里和彦, 杉本浩一, 竹石恭知	ボセンタンにエポプロステノール持続静注療法を追加することで病態が改善した特発性肺動脈性肺高血圧症の2例	Modern Physician	30 (臨時増刊)	96-99	2010
	大竹 敦, 本間俊彦, 酒井一吉, 油井徳雄, 斎藤修一, 竹石恭知	外来高血圧症例の早朝血圧調節不良例に対するアンジオテンシンⅡ受容体拮抗薬テルミサルタンの投与効果	Therapeutic Research	31 (2)	199-204	2010
	義久精臣, 杉本浩一, 三阪智史, 安藤勝也, 佐藤崇匡, 金城貴士, 小林淳, 國井浩行, 斎藤修一, 石橋敏幸, 横山 斉, 竹石恭知	不完全型房室中隔欠損症の術後約30年でdiscrete subaortic stenosisをきたした1症例	心臓	42 (8)	1072-1078	2010
	中里和彦, 木島幹博, 長澤脩一, 小山菊雄, 太田保世, 丸山幸夫, 竹石恭知	福島県急性心筋梗塞発症登録調査2009年集計	福島県医師会報	72 (7)	464-469	2010
	竹石恭知	CRP in assessment and management of CVD risk	AHA Highlight 2009		98-99	2010
	石橋敏幸, 杉本浩一, 竹石恭知	特集: RAGE: 心血管代謝病の新しい診断・治療標的 血管細胞におけるRAGE情報伝達機構	血管医学	11 (1)	11-19	2010
	中里和彦, 竹石恭知	DES時代の内科側からみたCABGの適応: 左主幹病変	日本冠疾患学会雑誌	16 (3)	211-218	2010
	鈴木 均, 竹石恭知	糖尿病と不整脈: 糖尿病が不整脈を引き起こすメカニズムはどのようにになっているのか?	Life Style Medicine	4 (4)	315-321	2010
	坂本信雄, 竹石恭知	たこつぼ心筋症の診断	心臓	42 (4)	441-450	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
竹石恭知	竹石恭知, 斎藤修一	心不全における炎症・免疫反応の重要性 — Toll-like receptorを介した細胞内シグナル活性化と梗塞後リモデリング	医学のあゆみ	232 (5)	378-385	2010
	神山美之, 鈴木均, 竹石恭知	循環器疾患の病態と診断・治療 (I) WPW症候群	医学と薬学	64 (5)	671-677	2010
	待井宏文, 竹石恭知	MRI・CT検査	Heart Nursing	23 (9)	933-938	2010
	小林 淳, 竹石恭知	心エコー検査	Heart Nursing	23 (9)	927-932	2010
	竹石恭知	心不全診療におけるバイオマーカー	Therapeutic Research	31 (7)	1010-1017	2010
川名正敏	JCS Joint Working Group	Guidelines for diagnosis and treatment of myocarditis (JCS 2009): digest version.	Circ J.	75 (3)	734-43	2011
	Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno K, Tanaka K, Kasanuki H, Takano T; ATTEND Investigators.	Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data.	Am Heart J.	159 (6)	949-955	2010
	Shiga T, Kasanuki H, Hagiwara N, Sumiyoshi T, Honda T, Haze K, Takagi A, Kawana M, Origasa H, Ogawa H; Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (Hij-Create) Investigators.	Angiotensin receptor blocker-based therapy and cardiovascular events in hypertensive patients with coronary artery disease and impaired renal function.	Blood Press.	19 (6)	359-65	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
廣 江 道 昭	1) Jesmin S, Mowa CN, Sultana SN, Mia S, Islam R, Zaedi S, Sakuma I, Hattori Y, Hiroe M, Yamaguchi N	Estrogen receptor alpha and beta are both involved in the cerebral VEGF/Akt/NO pathway and cerebral angiogenesis in female mice.	Biomed Res	31	337-346	2010
	2) Jesmin S, Mowa CN, Sultana SN, Shimojo N, Togashi H, Iwashima Y, Kato N, Sato A, Sakuma I, Hiroe M, Hattori Y, Yamaguchi N, Kobayashi H	VEGF signaling is disrupted in the hearts of mice lacking estrogen receptor alpha.	Eur J Pharmacol	641	168-178	2010
	3) Taki J, Inaki A, Wakabayashi H, Imanaka-Yoshida K, Ogawa K, Hiroe M, Shiba K, Yoshida T, Kinuya S	Dynamic expression of tenascin-C after myocardial ischemia and reperfusion: Assessment by I-125-anti tenascin-C antibody imaging	J Nucl Med	51	1116-1122	2010
	4) Sato A, Ohigashi H, Nozato T, Hikita H, Tamura M, Miyazaki S, Takahashi Y, Kuwahara T, Takahashi A, Hiroe M, Aonuma K	Coronary artery spatial distribution, morphology, and composition of nonculprit coronary plaques by 64-slice computed tomographic angiography in patients with acute myocardial infarction.	Am J Cardiol	105	930-935	2010
	5) Nishioka T, Onishi K, Shimojo N, Nagano Y, Matsusaka H, Ikeuchi M, Ide T, Tsutsui H, Hiroe M, Yoshida T, Imanaka-Yoshida K	Tenascin-C may aggravate left ventricular remodeling and function after myocardial infarction in mice	Am J Physiol Heart Circ Physiol	298	H1072-H1078	2010
	6) Sato A, Nozato T, Hikita H, Miyazaki S, Takahashi Y, Kuwahara T, Takahashi A, Hiroe M, Aonuma K	Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease	J Nucl Cardiol	17	19-26	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
廣江道昭	7) Hirakata H, Tsubakihara Y, Gejyo F, Nishi S, Ino Y, Watanabe Y, Suzuki M, Saito A, Akiba T, Inaguma D, Fukuhara S, Morita S, Hiroe M, Hada Y, Suzuki M, Akaishi M, Aonuma K, Akizawa T	Maintaining high hemoglobin levels improved the left ventricular mass index and quality of life scores in pre-dialysis Japanese chronic kidney disease patients	Clin Exp Nephrol	14	28-35	2010
	8) Katashima T, Naruko T, Terasaki F, Fujita M, Otsuka K, Murakami S, Sato A, Hiroe M, Ikura Y, Ueda M, Ikemoto M, Kitaura Y	Enhanced expression of the S100A8/A9 complex in acute myocardial infarction patients.	Circ J	74	741-748	2010
	9) Takeuchi F, Kashida M, Okazaki O, Tanaka Y, Fukuda S, Kashima T, Hosaka S, Hiroe M, Kimura S, Kato N	Evaluation of Pharmacogenetic Algorithm for Warfarin Dose Requirements in Japanese Patients.	Circ J	74	977-982	2010
	10) Tokyo CCU Network Scientific Committee	Latest management and outcomes of major pulmonary embolism in the cardiovascular disease early transport system: Tokyo CCU Network.	Circ J	74	289-293	2010
	遠藤久子、廣江道昭	メタボリックシンドロームと心筋病変—特に糖尿病性心筋症を中心に—	病理と臨床	29	249-253	2011
木村彰方	<u>Kimura A</u>	Molecular basis of hereditary cardiomyopathy: abnormalities in calcium sensitivity, stretch response, stress response and beyond.	J Hum Genet	55(2)	81-90	2010
	Arimura T, Sato R, Machida N, Bando H, Zhang DY, Morimoto S, Tanaka R, Yamane Y, Bonne G, <u>Kimura A</u>	Improvement of left ventricular dysfunction and of survival prognosis of dilated cardiomyopathy by administration of calcium sensitizer SCH00013 in a mouse model.	J Am Coll Cardiol	55(14)	1503-1505	2010
	Choi JO, You CW, Nah JC, Park JR, Lee BS, Choi BY, Cho BY, Lee SC, Park SW, <u>Kimura A</u> , Park JE	Long-term outcome of four Korean families with hypertrophic cardiomyopathy caused by four different mutations.	Clin Cardiol	33(7)	430-438	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
木村彰方	Hitomi N, Kubo T, Kitaoka H, Hirota T, Hamada T, Hoshikawa E, Hayato K, Okawa M, <u>Kimura A</u> , Doi YL	A frameshift deletion mutation in the cardiac myosin-binding protein C gene was associated with dilated phase of hypertrophic cardiomyopathy and dilated cardiomyopathy.	J Cardiol	56(2)	189-196	2010
	Purevjav E, Varela J, Morgado M, Kearney DL, Li H, Taylor MD, Arimura T, Moncman CL, McKenna W, Labeit S, Vatta M, Bowles NE, <u>Kimura A</u> , Boriek AM, Towbin JA	Nebulette mutations are associated with dilated cardiomyopathy and endocardial fibroelastosis.	J Am Coll Cardiol	56(18)	1493-1502	2010
	hichi D, Arimura T, Ishikawa T, <u>Kimura A</u>	Heart-specific small subunit of myosin light chain phosphatase activates Rho-associated kinase and regulates phosphorylation of myosin phosphatase target subunit 1.	J Biol Chem	285(44)	33680-33690	2010
	Li Z, Ai T, Samani K, Xi Y, Tzeng HP, Xie M, Taylor MD, Wu S, Ge S, Dong JW, Cheng J, Ackerman MJ, <u>Kimura A</u> , Sinagra G, Brunelli L, Faulkner G, Vatta M	A ZASP missense mutation, S196L, leads to cytoskeletal and electrical abnormalities in a mouse model of cardiomyopathy.	Circ Arrhythm Electrophysiol	3(6)	646-656	2010
室原豊明	Inden Y, Ito R, Yoshida N, Kamiya H, Kitamura K, Kitamura T, Shimano M, Uchikawa T, Tsuji Y, Shibata R, Hirai M, Murohara T.	Combined assessment of left ventricular dyssynchrony and contractility by speckled tracking strain imaging: A novel index for predicting responders to cardiac resynchronization therapy.	Heart Rhythm	7(5)	655-661	2010
	Shimano M, Ouchi N, Shibata R, Ohashi K, Pimentel DR, Murohara T, Walsh K.	Adiponectin deficiency exacerbates cardiac dysfunction following pressure overload through disruption of an AMPK-dependent angiogenic response.	J. Mol. Cell. Cardiol.	49(2)	210-220	2010
	Kondo K, Shibata R, Unno K, Shimano M, Ishii M, Tetsutaro K, Shintani S, Walsh K, Ouchi N, Murohara T.	Impact of a Single Intracoronary Administration of Adiponectin on Myocardial Ischemia/Reperfusion Injury in a Pig Model.	Circ. Cardiovasc. Interv.	3(2)	166-173	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
室原豊明	Yamada S, Ishii H, Takahashi H, Aoyama T, Morita Y, Kasuga H, Kimura K, Ito Y, Takahashi R, Toriyama T, Yasuda Y, Hayashi M, Kamiya H, Yuzawa Y, Maruyama S, Matsuo S, Matsubara T, Murohara T.	Prognostic value of reduced left ventricular ejection fraction at start of hemodialysis therapy on cardiovascular and all-cause mortality in end-stage renal disease patients.	Clin. J. Am. Soc. Nephrol.	5(10)	1793-1798	2010
	Ando, K., , Takahashi, M., Yamagishi, T., Miyagawa-Tomita, S., Imanaka-Yoshida, Toshimichi Yoshida, K., Nakajima, Y.	Tenascin C may regulate the recruitment of smooth muscle cells during coronary artery development.	Differentiation	in press		
	Okamoto, H. and Imanaka-Yoshida, K.	Matricelular proteins- New molecular targets to prevent heart failure.	Cardiovasc. Ther.	in press		
	Ishigaki, T., Imanaka-Yoshida, K., Shimojo, N., Matsushima, S., Taki, W., and Yoshida, T.	Tenascin-C enhances crosstalk signaling of integrin alphavbeta3/PDGFR-beta complex by SRC recruitment promoting PDGF-induced proliferation and migration in smooth muscle cells.	J Cell Physiol	28	Epub ahead of prints	2010
今中恭子	Nagaharu, K., Zhang, X., Yoshida, T., Katoh, D., Hanamura, N., Kozuka, Y., Ogawa, T., Shiraishi, T., and Imanaka-Yoshida, K.	Tenascin C induces epithelial-mesenchymal transition-like change accompanied by SRC activation and focal adhesion kinase phosphorylation in human breast cancer cells.	Am J Pathol	178	754-63	2011
	Hanato, T., Nakagawa, M., Okamoto, N., Nishijima, S., Fujino, H., Shimada, M., Takeuchi, Y., and Imanaka-Yoshida, K.	Developmental defects of coronary vasculature in rat embryos administered bis-diamine.	Birth Defects Res B Dev Reprod Toxicol.	92	10-16	2011
	Taki, J., Inaki, A., Wakabayashi, H., Imanaka-Yoshida, K., Ogawa, K., Hiroe, M., Shiba, K., Yoshida, T., and Kinuya, S.	Dynamic expression of tenascin-C after myocardial ischemia and reperfusion: assessment by 125I-anti-tenascin-C antibody imaging.	J Nucl Med.	51	1116-22	2010
	今中恭子	テネイシンCの役割	総合臨床	59	1725-1728	2010
	今中恭子	心筋炎	病理と臨床	29	126-131	2010

班員	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
大津欣也	Manabu Taneike, Osamu Yamaguchi, Atsuko Nakai, Shungo Hikoso, Toshihiro Takeda, Isamu Mizote, Takafumi Oka, Takahito Tamai, Jota Oyabu, Tomokazu Murakawa, Kazuhiko Nishida, Takahiko Shimizu, Masatsugu Hori, Issei Komuro, Takuji Shirasawa, Noboru Mizushima, Kinya Otsu	: Inhibition of autophagy in the heart induces age-related cardiomyopathy	Autophagy	6	1月7日	2010
石坂信和	Iimori A, Kanzaki Y, Ito S, Kotani T, Hirano-Kuwata S, Daimon M, Katsumata T, Akagi H, Komori T, Terasaki F, Ishizaka N, Ukimura A.	Rapidly progressive aneurysm of infected thoracic aorta with pseudoaneurysm formation.	Intern Med	49	2461-2465	2010
	Kanzaki Y, Terasaki F, Okabe M, Fujita S, Katashima T, Otsuka K, Ishizaka N.	Three-dimensional architecture of cardiomyocytes and connective tissue in human heart revealed by scanning electron microscopy.	Circulation	122	1973-1974	2010
	寺崎文生、神崎裕美子、石坂信和	拡張型心筋症	病理と臨床	29	119-125	2011
	寺崎文生、藤田修一、神崎裕美子、石坂信和	ARVC/Dの組織像、関連遺伝子と構造異常	不整脈News & Views	30	11-13	2010
	藤田修一、寺崎文生、宮村昌利、梅田達也、石坂信和	不整脈源性右室心筋症	総合臨牀	59	1719-1724	2010



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Identification of genes related to heart failure using global gene expression profiling of human failing myocardium

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ABSTRACT

Although various management methods have been developed for heart failure, it is necessary to investigate the diagnostic or therapeutic targets of heart failure. Accordingly, we have developed different approaches for managing heart failure by using conventional microarray analyses. We analyzed gene expression profiles of myocardial samples from 12 patients with heart failure and constructed datasets of heart failure-associated genes using clinical parameters such as pulmonary artery pressure (PAP) and ejection fraction (EF). From these 12 genes, we selected four genes with high expression levels in the heart, and examined their novelty by performing a literature-based search. In addition, we included four G-protein-coupled receptor (GPCR)-encoding genes, three enzyme-encoding genes, and one ion-channel protein-encoding gene to identify a drug target for heart failure using *in silico* microarray database. After the *in vitro* functional screening using adenovirus transfections of 12 genes into rat cardiomyocytes, we generated gene-targeting mice of five candidate genes, namely, *MYLK3*, *GPR37L1*, *GPR35*, *MMP23*, and *NBC1*. The results revealed that systolic blood pressure differed significantly between *GPR35*-KO and *GPR35*-WT mice as well as between *GPR37L1*-Tg and *GPR37L1*-KO mice. Further, the heart weight/body weight ratio between *MYLK3*-Tg and *MYLK3*-WT mice and between *GPR37L1*-Tg and *GPR37L1*-KO mice differed significantly. Hence, microarray analysis combined with clinical parameters can be an effective method to identify novel therapeutic targets for the prevention or management of heart failure.

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Introduction

Heart failure is a multi-factorial condition with increasing prevalence worldwide; further, a significant increase has been observed in the mortality rate and economic impact associated with this condition. In the last 20 years, substantial development of treatment for heart failure, including angiotensin-converting-enzyme inhibitors [1] and beta-blockers [2,3], has greatly improved the

prognosis of the patients with heart failure. However, despite these rapid advancements in the management of heart failure, effective treatment of end-stage heart failure without providing ventricular assistance or heart transplantation is still difficult. Investigation of new and unexplored targets for the prevention or treatment of heart failure is warranted. Global gene expression analysis using microarray technique has been used in the last decade to identify biomarkers or drug targets for heart failure [4–10]. Several gene expression signatures of heart failure have been identified by analyzing independent microarray datasets [11,12]. However, most of these analyses did not consider the severity of heart failure. Because the severity of heart failure may quantitatively reflect the expression levels of genes such as the natriuretic

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peptide-encoding gene, expression analysis combined with the severity of heart failure could be an appropriate method to identify heart failure-related genes. However, microarray analysis of genes expressed in failing myocardium while considering the severity of heart failure has not yet been reported.

Hence, we investigated the genes whose expression level correlated with clinical parameters such as pulmonary artery pressure (PAP), left ventricular ejection fraction (EF), and brain natriuretic peptide (BNP) mRNA level. Using this approach, we identified cardiac myosin light chain kinase as a novel heart failure-related gene [13]. Here, we describe newly identified several genes whose expression correlated with clinical parameters and additional genes encoding G-protein-coupled receptor genes (GPCRs), other enzymes and ion-channel proteins, and performed the functional analysis of these heart failure-related genes. This novel strategy involving the use of clinical parameters might find potential applications for the identification of disease-associated genes that could not be detected using conventional microarray techniques.

Materials and methods

Patient characteristics. We recruited 12 patients (11 males and 1 female) with heart failure and obtained written informed consent from them. The patients were diagnosed with severe chronic heart failure due to various cardiac diseases such as dilated cardiomyopathy and myocardial infarction [13]. The average age of patients was 55 ± 13 years. The plasma level of BNP, which is the best marker for the severity of heart failure, ranged from 80 to 2710 pg/ml. The mean PAP measured using a Swan-Ganz catheter 1–4 weeks before the operation varied between 16 and 59 mmHg. The average of EF determined by echocardiography on the day before the operation was $32.5\% \pm 12.4\%$.

Microarray analysis and subsequent in silico functional analysis. RNA was extracted from myocardium samples of 12 heart failure patients who had undergone either Batista or Dor surgeries. RNA samples of non-failing hearts were purchased from Biochain, Inc. Complementary RNA (cRNA) was prepared from RNA samples and hybridized to HG-U95 Affymetrix GeneChip (Affymetrix, US). The expression data were analyzed using Microarray Analysis Suite version 5.0 software. Among all the genes detected on the microarray, we selected the genes whose expression was significantly different in the failing and non-failing myocardial samples ($p < 0.005$). From these genes, we selected genes whose expression was correlated with PAP, EF, and BNP mRNA level, with 0.7 being the cutoff value of the correlation coefficient. The values of PAP, EF, and BNP mRNA level used for the correlation analysis were normalized to their median during the measurements. Subsequently, the functional analysis of datasets was performed using Ingenuity Pathway Analysis (Ingenuity® Systems; www.ingenuity.com), and the biological functions most significant to the dataset were identified.

Cell culture. Cardiomyocytes were harvested before the experiments from 2- to 3-day-old neonatal rats and cultured as described in previous studies [14]. Briefly, primary cardiomyocytes isolated from neonatal rats were grown in Dulbecco's modified Eagle medium/F12 (Gibco) supplemented with 10% fetal calf serum for 72 h, and then cultured in a serum-free condition for 24 h.

Adenovirus generation and transfection. Adenovirus constructs encoding the genes of interest were generated using the ViraPower Adenoviral Expression System (Invitrogen, US) according to the manufacturer's method. Adenovirus vectors were transfected to cultured cardiomyocytes for 12 h according to the published protocol.

In vitro functional analysis of genes. Cultured rat cardiomyocytes were infected by adenovirus vectors. After 24 h, hypertrophic

reaction, cell viability, and cellular morphology were assessed. Hypertrophic reaction was determined by estimating the incorporation of [³H]phenylalanine. In brief, [³H]phenylalanine was added to the culture medium at the final concentration of 0.1 μ Ci/ml, and the cells were incubated for an additional 24 h. Then, the incorporation of [³H]phenylalanine was determined by counting the radioactivity of each sample with a liquid scintillation counter. The viability of cardiomyocytes was evaluated by the Alamar blue assay according to the manufacturer's method. The morphology of cardiomyocytes was evaluated 24 h after adenovirus transfections.

Generation of transgenic and knockout mice. To generate transgenic mice, open reading frame of each gene, namely, *Mylk3*, *Gpr3711*, or *Nbc1* was amplified from mouse cDNA by PCR, with Sal I site linker on each end, and cloned into Sal I site of alpha-MHC clone 26 vector. Then the DNAs used in the microinjections were released from the vector by digestion with NotI and were microinjected into fertilized eggs of mouse. Founder mice were identified by PCR analysis with appropriate primers. To develop *Gpr3711* knockout mice, the targeting vector was assembled to replace the exon 1 and 2 by neomycin selection cassette resulting in the absence of *Gpr3711* protein. W9.5 ES cells were electroporated with linearized targeting vector. ES cell clones with successful homologous recombination was determined by the PCR and subsequent direct sequence. From these targeted ES cells, the chimera mice were bred to C57 BL/6 females to generate F1 and F2 offsprings were obtained. The *Gpr3711* null mice were determined by PCR genotyping of F2 offsprings. The knockout mice of *Gpr35* and *Mmp23* (the mouse ortholog of MMP23B) were purchased from Deltagen, Inc. (California, US).

Invasive blood pressure measurement. The phenotype of the gene-targeted mice was examined. Before sacrificing the mice, their hemodynamic parameters were evaluated. The mice were anesthetized and ventilated, and a Millar catheter was inserted via right carotid artery. The left-ventricular systolic and end-diastolic pressures were measured. Then, the mice were sacrificed and the weight of the whole body and heart was determined.

Statistical analysis. Unpaired Student's *t*-test was used for comparing the two groups. Results are expressed as means \pm SEM, and *p* value less than 0.05 was considered statistically significant.

Results

Identification of heart failure-related genes by expression analysis using clinical parameters

We performed microarray analysis of the genes expressed in failing myocardium obtained from 12 patients with heart failure and the genes expressed in non-failing myocardium from two normal objects whose characteristics were reported in the previous study [13]. Although all patients were diagnosed with chronic heart failure, the plasma BNP level, which is an index of the severity of heart failure, ranged from 80 to 2710 pg/ml, suggesting that the severity of heart failure varied extensively among the patients. This marked difference in the severity of heart failure reflects the fact that the gene expression patterns in the 12 patients were not uniform, as shown in Fig. 1A. Thus, we analyzed gene expression profiles of failing myocardium using clinical parameters representing the severity of heart failure. We identified 166 and 194 genes whose expressions were correlated with PAP and BNP mRNA level, respectively (Fig. 1B and Supplementary Tables S1, S2). Among these, 49 genes correlated with both PAP and BNP mRNA level (Fig. 1C). The expression of only two genes, namely, *FMO2* and *LMAN1L*, correlated with the EF. We investigated the functional categories of these genes by performing Ingenuity Pathway Analysis. The number of genes in each group, functional categories, and