## Cardiovascular Science Research Projects 2015

| Supervisors | | Project |
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| Prof Shoumo Bhattacharya | Dr Akane Kawamura | **Project title:** *BMP-signalling and cardiac fibrosis*<br><br>**Relevant publications:**<br>(1) van Meeteren LA, ten Dijke P. 2012. Regulation of endothelial cell plasticity by TGF-β. Cell Tissue Res., 347 (1), pp. 177-86.<br>(2) Krenning G, Zeisberg EM, Kalluri R. 2010. The origin of fibroblasts and mechanism of cardiac fibrosis. J. Cell. Physiol., 225 (3), pp. 631-7.<br>(3) Kovacic JC, Mercader N, Torres M, Boehm M, Fuster V. 2012. Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease. Circulation, 125 (14), pp. 1795-808. (4) Zuber J, McJunkin K, Fellmann C, Dow LE, Taylor MJ, Hannon GJ, Lowe SW. 2011. Toolkit for evaluating genes required for proliferation and survival using tetracycline-regulated RNAi. Nat. Biotechnol., 29 (1), pp. 79-83 |
| Prof Shoumo Bhattacharya | Dr Akane Kawamura | **Project title:** *Cyclic peptide inhibitors of TGFbeta signalling* |
| Prof Barbara Casadei | | **Project title:** *Role of microRNAs on atrial fibrillation induced myocardial remodelling*<br><br>**Relevant publications:**<br>(1) Luo X, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao L, Maguy A, Qi XY, LiY, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. J Clin Invest. 2013 May 1;123(5):1939-51.<br>(2) Lu Y, Zhang Y, Wang N, Pan Z, Gao X, Zhang F, Zhang Y, Shan H, Luo X, Bai Y, Sun L, Song W, Xu C, Wang Z, Yang B. MicroRNA-328 contributes to adverse electrical remodeling in atrial fibrillation. Circulation. 2010 Dec 7;122(23):2378-87. |

| Supervisors | | Project |
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| Prof Keith Channon | Dr Charalambos Antoniades | **Project title:** *Exploring a novel cross-talk between adipose tissue and vascular redox signalling*<br><br>**Relevant publications:**<br>(1) Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, Shirodaria C, Sayeed R, Petrou M, De Silva R, Jalilzadeh S, Demosthenous M, Bakogiannis C, Tousoulis D, Stefanadis C, Choudhury RP, Casadei B, Channon KM, Antoniades C. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. Circulation. 2013 Jun 4;127(22):2209-21<br>(2) Antoniades C, Bakogiannis C, Leeson P, Guzik TJ, Zhang MH, Tousoulis D, Antonopoulos AS, Demosthenous M, Marinou K, Hale A, Paschalis A, Psarros C, Triantafyllou C, Bendall J, Casadei B, Stefanadis C, Channon KM. Rapid, direct effects of statin treatment on arterial redox state and nitric oxide bioavailability in human atherosclerosis via tetrahydrobiopterin-mediated endothelial nitric oxide synthase coupling. Circulation. 2011 Jul 19;124(3):335-45. |
| Prof Robin Choudhury | | **Project title:** *Characterisation of monocyte function from peripheral blood of patients with type 2 diabetes: relationship to microvascular and macrovascular complications*<br><br>**Relevant publications:**<br>(1) Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. **Swirski** FK, **Nahrendorf** M. Science. 2013 Jan 11;339(6116):161-6. doi: 10.1126/science.1230719. Review.<br>(2) An unbalanced monocyte polarisation in peripheral blood and bone marrow of patients with type 2 diabetes has an impact on microangiopathy. Fadini GP, de Kreutzenberg SV, Boscaro E, Albiero M, Cappellari R, Kränkel N, Landmesser U, Toniolo A, Bolego C, Cignarella A, Seeger F, Dimmeler S, Zeiher A, Agostini C, Avogaro A. Diabetologia. 2013 Aug;56(8):1856-66. doi: 10.1007/s00125-013-2918-9. Epub 2013 Apr 26. PMID: 23616239 |

| Supervisors | | Project |
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| [Prof Kieran Clark] | | **Project title:** *Dietary Ketones and Heart Failure*<br><br>**Relevant publications:**<br>(1) IUBMB Life, 51: 241–247, 2001 Ketone Bodies, Potential Therapeutic Uses; Richard L. Veech, Britton Chance, Yoshihiro Kashiwaya, Henry A. Lardy and George F. Cahill, Jr.<br>(2) FASEB Journal article fj.11-200410; Mitochondrial biogenesis and increased uncoupling protein 1 in brown adipose tissue of mice fed aketone ester diet; Shireesh Srivastava, Yoshihiro Kashiwaya, M.Todd King, Ulrich Baxa, Joseph Tam, Gang Niu, Xiaoyuan Chen, Kieran Clarke and Richard L Veech<br>(3) Regulatory Toxicology and Pharmacology 63 (2012) 401–408; Kinetics, safety and tolerability of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate in healthy adult subjects; Kieran Clarke , Kirill Tchabanenko, Robert Pawlosky, Emma Carter, M. Todd King, Kathy Musa-Veloso, Manki Ho, Ashley Roberts, Jeremy Robertson, Theodore B. VanItallie, Richard L. Veech |
| [Prof Chris Garland] | | **Project title:** *Endothelial cell control of arterial tone*<br><br>**Relevant publications:**<br>(1) EDHF: spreading the influence of the endothelium. Garland CJ, Hiley CR, Dora KA.Br J Pharmacol. 2011 Oct;164(3):839-52<br>(2) Low intravascular pressure activates endothelial cell TRPV4 channels, local Ca2+ events, and IKCa channels, reducing arteriolar tone. Bagher P, Beleznai T, Kansui Y, Mitchell R, Garland CJ, Dora KA. Proc Natl Acad Sci USA. 2012 Oct 15. |
| [Prof David R Greaves] | | **Project title:** Identification and analysis of M2 polarised macrophages in vivo<br><br>**Relevant publications:**<br>(1) Williams HJ, Fisher EA, Greaves DR.<br>crophage differentiation and function in atherosclerosis: opportunities for therapeutic intervention?<br>nate Immun. 2012; 4: 498-508.<br><br>(2) Iqbal AJ, McNeill E, et al<br>man CD68 promoter directs GFP transgene expression in mouse myeloid cells, allowing analysis of monocyte to<br>crophage differentiation in vivo. |

| Supervisors | | Project |
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| Dr Lisa Heather | | **Project title:** *Metabolism and function in the Diabetic and Infarcted Heart*<br><br>**Relevant publications:**<br>(1)Heather LC and Clark K. Metabolism, Hypoxia and the Diabetic Heart. J Mol Cell Cardiol, 2011, 50: 598-605<br>(2)Heather LC et al. Differential translocation of the fatty acid transporter, FAT/CD36, and the glucose transporter, GLUT4, coordinates changes in cardiac substrate metabolism during ischemia and reperfusion. Circ Heart Failure, 2013, 6: 1059-66<br>Boudina s and Abel ED. Daibetic Cardiomyopathy revisited. Circulation, 2007, 26: 3213-23<br>. |
| Prof Paul Leeson | | **Project title:** *Prevention of cardiovascular disease in mother and child following preeclampsia*<br><br>**Relevant publication:**<br>Davis EF, Newton L, Lewandowski AJ, Lazdam M, Kelly BA, Kyriakou T, Leeson P. 2012. Pre-eclampsia and offspring cardiovascular health: mechanistic insights from experimental studies. Clin. Sci., 123 (2), pp. 53-72 |
| Dr Ming Lei | | **Project title:** *P21 activated kinase signalling in cardiac function, disease and therapy*<br><br>**Relevant publication:**<br>(1) Ke YB, Lei M, Collins TP, Rakovic S, Mattick P, Yamasaki M, Brodie MS, Terrar DA & Solaro RJ. Regulation of L-type calcium channel activity by $^{P21}$ activated kinase-1 in guinea-pig sino-trial node pacemaker cells. *Circ Res.* 2007; 100: 1317-27.<br><br>(2) Liu W, Zi M, Naumann R Ulm S, Jin J, Taglieri DM; Prehar S, Gui J, Tsui H, Xiao R, Neyses L, Solaro RJ, Ke Y, Cartwright EJ, Lei M & Wang X. Pak1 as a Novel Therapeutic Target for Anti-Hypertrophic Treatment in the Heart, *Circulation.* 2011;124:2702-15<br><br>(3) Liu W, Zi M, Tsui H, Chowdhury SK, Zeef L, Meng Q, Travis M, Prehar S, Berry A, Hanley N, Neyses L, Xiao R, Oceandy D, Ke Y, Solaro RJ, Cartwright EJ, Lei M and Wang X. A novel immunomodulator, FTY-720 reverses existing cardiac hypertrophy and fibrosis from pressure overload by targeting NFAT signaling and periostin. *Circulation Heart Fail.* 2013; 6(4):833-44<br><br>(4) Wang Y, Tsui H, Liu W, Shi Y, Wang R, Zhang Y, Solaro R, Ke Y, Zhang H, Cartwright E, Wang X and Lei M. P21 activated kinase-1 deficiency in cardiomyocytes increases in susceptibility to ventricular arrhythmogenesis in mice. *Circulation: Arrhythm Electrophysiol* 2014 (in press) |

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| Prof Stefan Neubauer | Dr Craig Lygate | **Project title:** *Assessing the therapeutic potential of augmenting cardiac energetics*<br><br>**Relevant publications:**<br>(1) Neubauer S. The failing heart--an engine out of fuel. New Engl J Med. 2007;356(11):1140-1151.<br>(2) Lygate CA, Bohl S, ten Hove M, Faller KM, Ostrowski PJ, Zervou S, Medway DJ, Aksentijevic D, Sebag-Montefiore L, Wallis J, Clarke K, Watkins H, Schneider JE, Neubauer S (2012) Moderate elevation of intracellular creatine by targeting the creatine transporter protects mice from acute myocardial infarction. Cardiovascular Research 96:466-475<br>(3) Lygate CA, Aksentijevic D, Dawson D, Ten Hove M, Phillips D, de Bono JP, Medway DJ, Sebag-Montefiore L, Hunyor I, Channon KM, Clarke K, Zervou S, Watkins H, Balaban RS, Neubauer S (2013) Living without creatine: unchanged exercise capacity and response to chronic myocardial infarction in creatine-deficient mice. Circulation Research 112:945-955 |
| Prof David Paterson | | **Project title:** *Neural control and arrhythmia: electrophysiological, imaging and gene transfer strategy*<br><br>**Relevant publications:**<br>(1) Li D, Nikiforova, N., Lu, C-J. Wannop, K., McMenamin, M., Lee CW, Buckler K, Paterson DJ. (2013). Targeted neuronal nitric oxide synthase transgene delivery into stellate neurons reverses impaired intracellular calcium transients in prehypertensive rats. *Hypertension* Jan;61(1):202-20<br>(2) Li, D., Lee, C.W., Buckler, K., Parekh, A., Herring, N. and Paterson, D.J. (2012) Abnormal Intracellular Calcium Homeostasis in Sympathetic Neurons From Young Prehypertensive Rats. *Hypertension* Mar;59(3):642-9 |
| Prof David Paterson | Dr Neil Herring | **Project title:** *The influence of neuropeptide Y on cardiac perfusion and arrhythmias*<br><br>**Relevant publications:**<br>(1) Shanks J, Herring N. (2013) Invited Review EB2012: Peripheral cardiac sympathetic hyperactivity: consequences in cardiovascular disease. *Am J Physiol (*DOI:10.1152/ajpregu.00118.2013) in press<br>(2) Cuculi F, Herring N, De Caterina AR, Banning AP, Prendergast BD, Forfar JC, Choudhury RP, Channon KM, Kharbanda RK. (2013) Relationship of plasma Neuropeptide Y with angiographic, electrocardiographic and coronary physiology indices of reperfusion during ST elevation myocardial infarction. *Heart* 99(16), 1198-203 (*See Editorial)* |
| Prof Roger Patient | | **Project title:** *Cardiac regeneration in zebrafish*<br><br>**Relevant publications:**<br>(1) Curr Top Dev Biol. 2012 100:319-44. Cardiac regeneration. Choi WY, Poss KD.<br>(2) Nature. 2010 464: 606-9. Zebrafish heart regeneration occurs by cardiomyocyte dedifferentiation and proliferation. Jopling C, Sleep E, Raya M, Martí M, Raya A, Izpisúa Belmonte JC.<br>(3) Development. 2011 138: 3235-45. Fgf differentially controls cross-antagonism between cardiac and haemangioblast regulators. Simoes FC, Peterkin T, Patient R |

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| Dr Charles Redwood | Dr. Katja Gehmlich | **Project title:** *The role of stretch signalling in Hypertrophic Cardiomyopathy*<br><br>**Relevant publications:**<br>(1) Geier C, Gehmlich K et al. Beyond the sarcomere: CSRP3 mutations cause hypertrophic cardiomyopathy. Hum Mol Genet. 2008, PMID:18505755<br>(2) Gehmlich K et al. Back to square one: what do we know about the functions of muscle LIM protein in the heart? J Muscle Res Cell Motil. 2008, PMID:19115046 |

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| Prof Paul Riley | | **Project title:** *Defining the role of epicardial signals in conditioning repair and regeneration of the injured heart*<br><br>**Relevant publications:**<br>(1) Riley PR. (2012). An epicardial floor plan for building and rebuilding the mammalian heart. Curr Top Dev Biol. 100:233-251. Review.<br>(2) Rossdeutsch A, Smart N, Dubé KN, Turner M, Riley PR. (2012). Essential role for thymosin β4 in regulating vascular smooth muscle cell development and vessel wall stability. Circ Res. 111:e89-102.<br>(3) Risebro CA, Petchey LK, Smart N, Gomes J, Clark J, Vieira JM, Yanni J, Dobrzynski H, Davidson S, Zuberi Z, Tinker A, Shui B, Tallini YI, Kotlikoff MI, Miquerol L, Schwartz RJ, Riley PR. (2012). Epistatic rescue of Nkx2.5 adult cardiac conduction disease phenotypes by prospero-related homeobox protein 1 and HDAC3. Circ Res. 111:e19-31.<br>(4) Smart N, Bollini S, Dubé KN, Vieira JM, Zhou B, Davidson S, Yellon D, Riegler J, Price AN, Lythgoe MF, Pu WT, Riley PR. (2011), De novo cardiomyocytes from within the activated adult heart after injury. Nature. 474:640-644. |
| Dr Jürgen Schneider | Dr Craig Lygate | **Project title:** *Multi-parametric Magnetic Resonance Imaging of the Remodelling Mouse Heart*<br><br>**Relevant publications:**<br>(1) Magn Reson Med. 2012 Jan; 67(1):191-200. doi: 10.1002/mrm.22973<br>(2) Magnetic Resonance in Medicine 2013 70:1095–1105 |

| Supervisors | | Project |
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| Prof Rebecca Sitsapesan | | **Project title:** *Physiological and pathological significance of trimeric intracellular cation (TRIC)-channel sensitivity to voltage and pH in the cardiovascular system*<br><br>**Relevant publications:**<br>(1) Venturi, E., Sitsapesan, R., Yamazaki, D. & Takeshima, H. (2013). TRIC channels supporting efficient Ca2+ release from intracellular stores. Pflugers Arch-Eur. J. Physiol. 465, 187-195.<br>(2) Yazawa, M., et al. (2007). TRIC channels are essential for Ca2+ handling in intracellular stores Nature 448, 78-82. Yamazaki D, et al. (2011). TRIC-A channels in vascular smooth muscle contribute to blood pressure maintenance. Cell Metab 14:231–241.<br>(3) Zhao X, Yamazaki D, Park KH, Komazaki S, Tjondrokoesoemo A, Nishi M, Lin P, Hirata Y, Brotto M, Takeshima H, Ma J (2010) Ca2+ overload and sarcoplasmic reticulum instability in tric-a null skeletal muscle. J Biol Chem 285:37370-37376.<br>(4) Yamazaki D, Komazaki S, Nakanishi H, Mishima A, Nishi M, Yazawa M, Yamazaki T, Taguchi R, Takeshima H (2009) Essential role of the TRIC-B channel in Ca2+ handling of alveolar epithelial cells and in perinatal lung maturation. Development 136:2355-2361. |
| Prof Rebecca Sitsapesan | Dr Paolo Tammaro | **Project title:** *Novel intracellular ion channels in the heart and their role in intracellular $Ca^{2+}$-release*<br><br>**Relevant publications:**<br>(1) Pitt, SJ, Lam, AKM, Rietdorf, K, Galione, A, and Sitsapesan, R (2014) Reconstituted Human TPC1 Is a Proton-Permeable Ion Channel and Is Activated by NAADP or $Ca^{2+}$. *Science Signal*, 7(326):ra46.<br><br>(2). Pitt, SJ, Funnell, TM, Sitsapesan, M, Venturi, E, Rietdorf, K, Ruas, M, Ganesan, A, Gosain, R, Churchill, GC, Zhu, MX, Parrington, J, Galione, A, and Sitsapesan, R (2010) TPC2 is a novel NAADP-sensitive $Ca^{2+}$ release channel, operating as a dual sensor of luminal pH and $Ca^{2+}$. *J Biol Chem*, 285(45):35039-46.<br><br>(3). Venturi, E., Sitsapesan, R., Yamazaki, D. & Takeshima, H. (2013). TRIC channels supporting efficient $Ca^{2+}$ release from intracellular stores. *Pflugers Arch-Eur. J. Physiol.* **465**, 187-195.<br><br>(4). Yazawa, M., et al. (2007). TRIC channels are essential for $Ca^{2+}$ handling in intracellular stores. *Nature* **448,** 78-82.<br>. |

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| Dr Nicola Smart | | **Project title:** *Approaches to enhance epicardial-based regeneration and vascular protection*<br><br>**Relevant publications:**<br>(1) Smart N, Bollini S, Dubé KN, Vieira JM, Zhou B, Davidson S, Yellon D, Riegler J, Price AN, Lythgoe MF, Pu WT, Riley PR. De novo cardiomyocytes from within the activated adult heart after injury. *Nature*. 2011; **474** (7353):640-4.<br>(2) Smart N, Risebro CA, Melville AA, Moses K, Schwartz RJ, Chien KR, Riley PR. Thymosin beta4 induces adult epicardial progenitor mobilization and neovascularization. *Nature*. 2007; **445** (7124):177-82<br><br>(3)Rossdeutsch A, Smart N, Dubé KN, Turner M, Riley PR. (2012). Essential role for thymosin β4 in regulating vascular smooth muscle cell development and vessel wall stability. Circ Res. 111:e89-102.<br>(4) Smart N, Risebro CA, Melville AA, Moses K, Schwartz RJ, Chien KR, Riley PR<br>(2007). Thymosin β4 induces adult epicardial progenitor mobilization and neovascularization. Nature 445 (7124): 177-82. |
| Dr Nicola Smart | Dr Carolyn Carr | **Project title:** *Tracing the origins and differentiation of cardiac progenitors, fibroblasts and myocytes*<br><br>**Relevant publications:**<br>(1) Carr CA, Stuckey DJ, Tan JJ, Tan SC, Gomes RSM, Camelitti P, Messina E, Giacomello A, Ellison GM, Clarke K; "Cardiosphere-derived mesenchymal cells improve function in the infarcted rat heart for at least 16 weeks – an MRI study", *PLoS ONE*, 2011 6, e25669<br>(2) Smart N, Bollini S, Dube KN, Vieira JM, Zhou B, Davidson S, Yellon D, Riegler J, Price AN, Lythgoe MF, Pu WT, Riley PR; "De novo cardiomyocytes from within the activated adult heart after injury." *Nature*, 2011, 474, 640 |
| Dr Paolo Tammaro | | **Project title:** *Using light to control blood vessels*<br><br>**Relevant publications:**<br>(1) Smith KJ, Chadburn AJ, Adomaviciene A, Minoretti P, Vignali L, Emanuele E, Tammaro P. (2013) Coronary spasm and acute myocardial infarction due to a mutation (V734I) in the nucleotide binding domain 1 of ABCC9. *Int J Cardiol*. *In press.*<br>(2) Adomaviciene A, Smith KJ, Garnett H, Tammaro P. (2013) Putative pore-loops of TMEM16/Anoctamin channels affect channel density in cell membranes. *J Physiol (Lond).* 591:3487-505. |

| Supervisors | | Project |
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| Dr Damian Tyler | | **Project title:** *Application of Hyperpolarized Magnetic Resonance Imaging for the Assessment of Treatment Response in the Diseased Heart*<br><br>**Relevant publications:**<br>(1) Hyperpolarized magnetic resonance: A novel technique for the in vivo assessment of cardiovascular disease. Circulation 124 (2011)<br>(2) Role of pyruvate dehydrogenase inhibition in the development of hypertrophy in the hyperthyroid rat heart: A combined magnetic resonance imaging and hyperpolarized magnetic resonance spectroscopy study. Circulation 123 (2011) |
| Prof Manuela Zaccolo | | **Project title:** *Cyclic nucleotide microdomains and cardiac pathophysiology*<br><br>**Relevant publication:**<br>Zaccolo M. Spatial control of cAMP signalling in health and disease. Curr Opin Pharmacol. 2011 Dec;11(6):649-55 |
| Prof Manuela Zaccolo | Dr Konstantinos Lefkimmiatis | **Project title:** *Mitochondrial cyclic AMP signalling in heart pathophysiology*<br><br>**Relevant publication:**<br>(1) Zaccolo M. Spatial control of cAMP signalling in heart and disease. Current Opinion in Pharmacology. 2011 Dec; 11(6):649-55 (http://www.ncbi.nlm.nih.gov/pubmed/22000603)<br>(2) Lefkimmiatis K, et al. Store-operated cyclic AMP signalling mediated by STIM1. Nature Cell Biology. 2009 Apr; 11(4):433-42 (http://www.ncbi.nlm.nih.gov/pubmed/19287379)<br>(3) Lefkimmiatis K, et al. The inner and outer compartments of mitochondria are sites of distinct cAMP/PKA signaling dynamics. Journal of Cell Biology. 2013 Aug; 5;202(3):453-62 (http://www.ncbi.nlm.nih.gov/pubmed/23897891) |