

CARDIOLOGY DIVISION PUBLICATIONS 2008

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Kenneth Chien, MD, PhD, Associate Chief
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Cardiology Clinical/Translational /Basic Research Publications:

Total publications: 282
Original articles: 182
Reviews/Chapters: 100

Key Publications:

Yu PB, Deng DY, Lai CS, Hong CC, Cuny GD, Bouxsein ML, Hong DW, McManus PM, Katagiri T, Sachidanandan C, Kamiya N, Fukuda T, Mishina Y, Peterson RT, Bloch KD. BMP type I receptor inhibition reduces heterotopic ossification. *Nat Med.* 2008 Dec;14(12):1363-9.

This paper is based on a novel discovery of a new BMP receptor antagonist that was isolated by chemical screening in a zebrafish model system, utilizing a library of compounds that were already approved for use in humans, and a readout that was based on the known ability of BMP to perturb the developmental morphogenic axis of zebrafish embryos. Following this discovery, a series of improvements in the initial compound were developed and utilized in a clever clinically relevant application to a rare bone ossification disorder that arises in children due to activating mutations in the BMP receptor. Paul Yu, on his own initiative, recognized this clinical niche application, and characterized a mouse model of the disease, which recapitulates key aspects of the disease phenotype. In a remarkable advance that has clear translational implications, he documented in this first author Nature Medicine paper that the onset of the bone defects was largely prevented, suggesting the clinical potential of this novel strategy. The work has led to a full scale medicinal chemistry effort to develop new specific BMP receptor antagonists (there are none known aside from this discovery to date), to take this work to children with this disorder, and to examine effects of these series of compounds in other diseases and biological systems where BMP signaling is known to play a pivotal role.

Kathiresan S, Melander O, Anevski D *et al.* Polymorphisms associated with cholesterol and risk of cardiovascular events. *NEJM* 2008;358(12):1240-1249.

This study demonstrated that a combination of several lipid-related polymorphisms stratified individuals across clinically meaningful ranges of blood lipids and predicted risk for cardiovascular disease above and beyond traditional risk factors. We provided proof-of-concept that a panel of polymorphisms may have clinical application in risk prediction.

Albert, CM, Nam, EG, Rimm, EB, Jin, HW, Hajjar, RJ, Hunter, DJ, MacRae, CA, Ellinor, PT. Cardiac Sodium Channel Gene Variants and Sudden Cardiac Death in Women. *Circulation*, 2008 Jan 1;117(1):16-23.

The ability to identify individuals who are at risk for sudden cardiac death (SCD) in the general population is poor. Although SCD risk has a heritable component, the extent to which the heritable component of more common forms of SCD might be due mutations or rare polymorphisms in cardiac ion channels is currently unknown. To address this question, this study sought to determine both the prevalence and function of mutations and rare coding sequence variants in 5 cardiac ion channel genes among cases of SCD drawn from 2 large prospective cohorts of women and men. The key finding was that the frequency of rare variants in the cardiac sodium channel was significantly higher in the SCD cases compared with controls. These data suggest that functionally significant rare variants in cardiac sodium channel may contribute to SCD risk in the general population.

Jaffer FA, Vinegoni C, John MC, Aikawa E, Gold HK, Finn AV, Ntziachristos V, Libby P, Weissleder R. Real-time catheter molecular sensing of inflammation in proteolytically active atherosclerosis. *Circulation*. 2008 Oct 28;118(18):1802-9.

This paper demonstrates the ability to sense inflammation in atherosclerotic plaques using clinical-type intravascular near-infrared fluorescence catheters for molecular imaging. This study provides a foundation for identifying high-risk, inflamed plaques.

Cardiovascular Research Center

A high-efficiency system for the generation and study of human induced pluripotent stem cells, Maherali N, Ahfeldt T, Rigamonti A, Utikal J, Cowan C, Hochedlinger K., *Cell Stem Cell*. 2008 Sep 11;3(3):340-5.

A non-canonical function of zebrafish telomerase reverse transcriptase is required for developmental hematopoiesis, Imamura S, Uchiyama J, Koshimizu E, Hanai J, Raftopoulou C, Murphey RD, Bayliss PE, Imai Y, Burns CE, Masutomi K, Gagos S, Zon LI, Roberts TM, Kishi S., *PLoS ONE*. 2008;3(10):e3364.

A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction, Kathiresan S; Myocardial Infarction Genetics Consortium., *N Engl J Med*. 2008 May 22;358(21):2299-300.

A short duration of high-fat diet induces insulin resistance and predisposes to adverse left ventricular remodeling after pressure overload, Raheer MJ, Thibault HB, Buys ES, Kuruppu D, Shimizu N, Brownell AL, Blake SL, Rieusset J, Kaneki M, Derumeaux G, Picard MH, Bloch KD, Scherrer-Crosbie M., *Am J Physiol Heart Circ Physiol*. 2008 Dec;295(6):H2495-502.

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Association of NOS1AP genetic variants with QT interval duration in families from the Diabetes Heart Study, Lehtinen AB, Newton-Cheh C, Ziegler JT, Langefeld CD, Freedman BI, Daniel KR, Herrington DM, Bowden DW., *Diabetes*. 2008 Apr;57(4):1108-14.

Bayesian meta-analysis of genetic association studies with different sets of markers, Verzilli C, Shah T, Casas JP, Chapman J, Sandhu M, Debenham SL, Boekholdt MS, Khaw KT, Wareham NJ, Judson R, Benjamin EJ, Kathiresan S, Larson MG, Rong J, Sofat R, Humphries SE, Smeeth L, Cavalleri G, Whittaker JC, Hingorani AD., *Am J Hum Genet*. 2008 Apr;82(4):859-72.

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BMP type I receptor inhibition reduces heterotopic ossification, Yu PB, Deng DY, Lai CS, Hong CC, Cuny GD, Bouxsein ML, Hong DW, McManus PM, Katagiri T, Sachidanandan C, Kamiya N, Fukuda T, Mishina Y, Peterson RT, Bloch KD., *Nat Med*. 2008 Dec;14(12):1363-9.

Bone morphogenetic protein (BMP) type II receptor is required for BMP-mediated growth arrest and differentiation in pulmonary artery smooth muscle cells, Yu PB, Deng DY, Beppu H, Hong CC, Lai C, Hoyng SA, Kawai N, Bloch KD., *J Biol Chem*. 2008 Feb 15;283(7):3877-88.

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Cardiac sodium channel mutation in atrial fibrillation, Ellinor PT, Nam EG, Shea MA, Milan DJ, Ruskin JN, MacRae CA., *Heart Rhythm*. 2008 Jan;5(1):99-105.

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Noninvasive in vivo imaging of monocyte trafficking to atherosclerotic lesions, Kircher MF, Grimm J, Swirski FK, Libby P, Gerszten RE, Allport JR, Weissleder R., *Circulation*. 2008 Jan 22;117(3):388-95.

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Polymorphisms associated with cholesterol and risk of cardiovascular events, Kathiresan S, Melander O, Anevski D, Guiducci C, Burt NP, Roos C, Hirschhorn JN, Berglund G, Hedblad B, Groop L, Altshuler DM, Newton-Cheh C, Orho-Melander M., *N Engl J Med*. 2008 Mar 20;358(12):1240-9.

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Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans, Kathiresan S, Melander O, Guiducci C, Surti A, Burt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M., *Nat Genet.* 2008 Feb;40(2):189-97. Epub 2008 Jan 13. Erratum in: *Nat Genet.* 2008 Nov;40(11):1384.

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Vitamin K and vitamin D status: associations with inflammatory markers in the Framingham Offspring Study, Shea MK, Booth SL, Massaro JM, Jacques PF, D'Agostino RB Sr, Dawson-Hughes B, Ordovas JM, O'Donnell CJ, Kathiresan S, Keaney JF Jr, Vasan RS, Benjamin EJ., *Am J Epidemiol.* 2008 Feb 1;167(3):313-20.

Chapters/Reviews/Editorials

Advances in fluorescence imaging of the cardiovascular system, Chang K, Jaffer F., *J Nucl Cardiol.* 2008 May-Jun;15(3):417-28. Review.

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Cardiogenesis and the complex biology of regenerative cardiovascular medicine, Chien KR, Domian IJ, Parker KK., *Science.* 2008 Dec 5;322(5907):1494-7. Review.

Challenges in translating plasma proteomics from bench to bedside: update from the NHLBI Clinical Proteomics Programs, Gerszten RE, Accurso F, Bernard GR, Caprioli RM, Klee EW, Klee GG, Kullo I, Laguna TA, Roth FP, Sabatine M, Srinivas P, Wang TJ, Ware LB., *Am J Physiol Lung Cell Mol Physiol*. 2008 Jul;295(1):L16-22. Epub 2008 May 2. Review.

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Deciphering arterial identity through gene expression, genetics, and chemical biology, Mukhopadhyay A, Peterson RT., *Curr Opin Hematol*. 2008 May;15(3):221-7. Review.

Defining the spectrum of alleles that contribute to blood lipid concentrations in humans, Kathiresan S, Musunuru K, Orho-Melander M., *Curr Opin Lipidol*. 2008 Apr;19(2):122-7. Review.

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Genetics of atrial fibrillation, Ellinor PT, Yi BA, MacRae CA., *Med Clin North Am*. 2008 Jan;92(1):41-51, x. Review.

Human embryonic stem cells: emerging technologies and practical applications, Fenno LE, Ptaszek LM, Cowan CA., *Curr Opin Genet Dev*. 2008 Aug;18(4):324-9

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Multipotent stem cells in cardiac regenerative therapy, Karra R, Wu SM., *Regen Med*. 2008 Mar;3(2):189-98.

Noninvasive imaging of apoptosis in cardiovascular disease, Korngold EC, Jaffer FA, Weissleder R, Sosnovik DE., *Heart Fail Rev*. 2008 Jun;13(2):163-73. Review.

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Polymorphisms and atrial fibrillation: sorting the wheat from the chaff, Ellinor PT, Milan DJ., *Eur Heart J*. 2008 Apr;29(7):843-5.

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Reversing advanced heart failure by targeting Ca²⁺ cycling, Kaye DM, Hoshijima M, Chien KR., *Annu Rev Med.* 2008;59:13-28. Review.

The search for new cardiovascular biomarkers, Gerszten RE, Wang TJ., *Nature.* 2008 Feb 21;451(7181):949-52. Review.

Toward biologically targeted therapy of calcium cycling defects in heart failure, Ikeda Y, Hoshijima M, Chien KR., *Physiology (Bethesda).* 2008 Feb;23:6-16. Review.

Use of non-mammalian alternative models for neurotoxicological study, Peterson RT, Nass R, Boyd WA, Freedman JH, Dong K, Narahashi T., *Neurotoxicology.* 2008 May;29(3):546-55. Epub 2008 Apr 25. Review.

Heart Failure/Cardiac Transplantation

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