Institute for Experimental Medical Research
and the national PhD School NORHEART

GUEST LECTURE

Wednesday December 13 at 9-10 a.m.

Grønt Auditorium, 1. etasje i Laboratoriebygget (bygg 25), OUS Ullevål

Professor Andrew Marks MD

Chair of the Physiology and Cellular Biophysics Department at Columbia University

"What makes the heart pump: high resolution structure and function of the ryanodine receptor"

Dr. Marks notably discovered that *"leaky" intracellular calcium release channels (ryanodine receptors) contribute to heart failure*, fatal cardiac arrhythmias, and impaired exercise capacity particularly in muscular dystrophy. Dr. Marks' investigations have defined how macromolecular signaling complexes regulate ion channel function, particularly in muscle, where his work has divulged fundamental mechanisms that regulate contraction. By developing a new class of small molecules (rycals) that fix the "leak" in ryanodine receptor/calcium release channels, Dr. Marks has demonstrated effective treatment of cardiac arrhythmias, heart failure and muscular dystrophy in pre-clinical studies, with Phase II clinical trials ongoing.

Dr. Marks' previous work on the mechanisms of action of drugs that inhibit vascular smooth muscle proliferation and migration has been translated into novel therapeutics including drug-eluting stents for the treatment of coronary artery disease. These advances have substantially reduced the incidence of in-stent restenosis, and reduced arteriopathy following cardiac transplantation.

CAREER SUMMARY

- MD, from Harvard Medical School 1980.
- Post-doctoral fellow and clinical cardiology fellow at Massachusetts General Hospital 1980-1987.
- Assistant Professor of Molecular Biology and Medicine at Mount Sinai School of Medicine 1990 .
- Fishberg Professor of Medicine at Mount Sinai 1995.
- Director of the Center for Molecular Cardiology and the Clyde and Helen Wu Professor of Medicine and Pharmacology at Columbia University College of Physician & Surgeons 1997.
- Professor of the Physiology and Cellular Biophysics Department at Columbia University 2003.
- Editor-in-Chief of the Journal of Clinical Investigation 2002-2007.
- Memberships in the American Society of Clinical Investigation, the American Association of Physicians, the Institute of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences.
- Chair of the SAB of ARMGO Pharma Inc., a company he founded in 2006 to develop novel therapeutics for heart and muscle diseases. Marks is the inventor on six U.S. patents for these new treatments.

SELECTED PUBLICATIONS

Brillantes AB, Ondrias K, Scott A, Kobrinsky E, Ondriasova E, Moschella MC, Jayaraman T, Landers M, Ehrlich BE, Marks AR. Stabilization of calcium release channel (ryanodine receptor) function by FK506-binding protein. Cell. 1994 May 20;77(4):513-23.

Jayaraman T, Ondrias K, Ondriasova E, Marks AR. Regulation of the inositol 1,4,5-trisphosphate receptor by tyrosine phosphorylation. Science. 1996 Jun 7;272(5267):1492-4.

Marx SO, Ondrias K, Marks AR. Coupled gating between individual skeletal muscle Ca2+ release channels (ryanodine receptors) Science. 1998 Aug 7;281(5378):818-21.

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Marx SO, Kurokawa J, Reiken S, Motoike H, D'Armiento J, Marks AR, Kass RS. Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. Science. 2002 Jan 18;295(5554):496-9.

Wehrens XH, Lehnart SE, Huang F, Vest JA, Reiken SR, Mohler PJ, Sun J, Guatimosim S, Song LS, Rosemblit N, D'Armiento JM, Napolitano C, Memmi M, Priori SG, Lederer WJ, Marks AR. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. Cell. 2003 Jun 27;113(7):829-40.

Wehrens XH, Lehnart SE, Reiken SR, Deng SX, Vest JA, Cervantes D, Coromilas J, Landry DW, Marks AR. Protection from cardiac arrhythmia through ryanodine receptor-stabilizing protein calstabin2. Science. 2004 Apr 9;304(5668):292-6.

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Bellinger, AM, Reiken, SR, Dura, M, Murphy, P, Deng, S-X, Neiman, D, Lehnart, S, Samaru, M, Lacampagne, A, and Marks, AR (2008) Remodeling of ryanodine receptor complex causes "leaky" channels: a molecular mechanism for decreased exercise capacity PNAS 105: 2198-2202

Bellinger, AM, Reiken, S, Carlson, C, Mongillo, M, Liu, X, Rothman, L, Matecki, S, LaCampagne, A, and Marks, AR (2009) Hypernitrosylated ryanodine receptor/calcium release channels are leaky in dystrophic muscle. Nature Medicine 15:325-330

Shan, J., Kushnir, A., Betzenhauser, M., Reiken, S., Li, J., Lehnart, S.E., Lindegger, N., Mongillo, M., Mohler, P.J., Marks, A.R. (2010) Phosphorylation of the Ryanodine Receptor Mediates the Cardiac Fight or Flight Response in Mice J. Clin. Invest. 120: 4375-87.

Shan, J., Betzenhauser, M., Kushnir, A., Reiken, S., Meli, A., Wronska, A., Dura, M., Chen, B.-X., Marks, A.R. (2010) Role of Chronic Ryanodine Receptor Phosphorylation in Heart Failure and Beta-adrenergic Receptor Blockade in Mice J. Clin. Invest. 120: 4388-98.

Andersson DC, Betzenhauser MJ, Reiken S, Meli AC, Umanskaya A, Xie W, Shiomi T, Zalk R, Lacampagne A, Marks AR. Ryanodine receptor oxidation causes intracellular calcium leak and muscle weakness in aging. Cell Metab. 2011 Aug 3;14(2):196-207. PMID: 21803290

Liu, X., Betzenhauser, M.J., Reiken, S., Meli, A.C., Arancio, O., Chen B.-X., Marks AR (2012) Role of Leaky Neuronal Ryanodine Receptors in Stress-Induced Cognitive Dysfunction Cell 150, 1055–1067.

Ran Zalk, Oliver B. Clarke, Amédée des Georges, Robert A. Grassucci, Steven Reiken, Filippo Mancia, Wayne A. Hendrickson, Joachim Frank, Marks, A.R. (2014) Structure of a mammalian ryanodine receptor Nature 2014 Dec 1. doi: 10.1038/nature13950.

Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, Chiechi A, Wright LE, Umanskaya A, Niewolna M, Trivedi T, Charkhzarrin S, Khatiwada P, Wronska A, Haynes A, Benassi MS, Witzmann FA, Zhen G, Wang X, Cao X, Roodman GD, Marks AR, Guise TA. Excess TGF-Beta mediates muscle weakness associated with bone metastases in mice. Nature Medicine, 2015 Oct 12 PMID:26457758

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