Keynote Lecture XI
Cardiac Muscle Cell Death and Regeneration

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Dr Michael Schneider is The MD Anderson Foundation Professor, Departments of Medicine, Molecular and Cellular Biology, and Molecular Physiology & Biophysics, at Baylor College of Medicine. He received his undergraduate training at Harvard, his MD from the University of Pennsylvania, and clinical training at Duke University. Dr Schneider received his post-doctoral research training at the National Insitutes of Health in the laboratories of Nobel laureate Marshall Nirenberg (Biochemical Genetics) and Robert Adelstein (Molecular Cardiology). He was recruited to Baylor in 1984, where he now serves as Director of the Center for Cardiovascular Development.

Dr Schneider has long been recognized internationally for his expertise on the molecular genetics of cardiac growth and heart failure. Dr Schneider's principal research themes include autocrine/paracrine circuits in cardiac development and hypertrophy, the molecular basis for ventricular muscle cells' irreversible exit from the cell cycle, and a recent focus on adult heart-derived progenitor cells for cardiac repair.

Dr Schneider was the recipient of the Lyndon Baines Johnson Award for Outstanding Research of the American Heart Associate Texas Affiliate, and an American Heart Association Established Investigator Award. He has been the presenter of invited lectures at Harvard, Penn, Duke, Johns Hopkins, Washington University, the University of Chicago, University of Michigan, University of Southern California, UCSF, UCLA, University of Toronto, University of Tokyo, the Max Delbrück Center for Molecular Medicine (Berlin), Biogen, Geron, Millennium, and Genzyme. He was twice an American Heart Association "State-of-the-Art Lecturer", and twice co-organizer of the Keystone Symposium in molecular cardiology.

Dr Schneider serves on the Editorial Boards of the *Journal of Clinical Investigation, Journal of Biological Chemistry,* and *Circulation Research.* He recently completed ten years as Associate Editor of *Circulation.* Dr Schneider has been a member of the National Institutes of Health Cardiovascular Study Section and has served on eighteen other NIH peer review panels. He currently serves on the Leadership Committee of the American Heart Association's Council on Basic Cardiovascular Sciences, chairs the AHA Louis and Arnold Katz Basic Science Research Prize, and was founding organizer of the AHA Annual Symposium on Basic Cardiovascular Sciences. He is currently Principal Investigator for three R01s, co-director of a Program Project on the molecular genetics of cardiac growth and differentiation, and US Coordinator for the Fondation Leducq Transatlantic Network of Excellence for Cardiac Regeneration.

Together, the limited capacity for regenerative growth in cardiac muscle after injury and the prevalence of ongoing sporadic cell death due to apoptosis even in chronic heart failure states pose one of the paramount challenges in heart failure therapeutics. In adults, the unique self-renewal potential of progenitor/stem cells is associated with telomerase reverse transcriptase (TERT), an RNA-dependent DNA polymerase that maintains the lariat-like loop (telomere) capping chromosome ends. We have identified multiple novel triggers of cell death in failing heart muscle, including telomere uncapping, activation of cyclin-dependent kinase-9, and

activation of the proximal MAP kinases TAK1 and HGK. Conversely, we sought a residual TERT+ population in adult myocardium, as a potential source of cardiac progenitor cells. Residual TERT expression was localized to cells expressing stem cell antigen-1 (Sca-1). Cardiac-resident Sca-1$^+$ cells lack hematopoietic stem cell markers and lack transcripts for cardiac structural genes, but express many cardiogenic transcription factors. If treated with 5'-azacytidine in culture, cardiac Sca-1$^+$ cells selectively activate more than 50 cardiac-restricted genes. If given intravenously to mice just after ischemia-reperfusion injury, cardiac Sca-1$^+$ cells home selectively to injured myocardium and differentiate robustly in situ, constituting ~15% of the myocytes in the border zone two weeks after grafting. These studies have identified multiple new "druggable targets" in heart failure, as well as pinpointing the heart itself as a source of progenitor cells with auspicious properties for cardiac regeneration.