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Editorial overview: Cardiovascular and renal: Novel therapeutic strategies and approaches for targeting unmet cardiovascular needs

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Gregory Kaczorowski graduated in Chemistry in 1972, obtained his PhD in Biochemistry from MIT in 1977 and was a Whitney Postdoctoral Fellow at the Roche Institute of Molecular Biology. He joined Merck in 1980 and later established and directed the Department of Ion Channels which focused on discovering modulators of voltage-gated potassium, calcium and sodium channels, as well as, of ligand-gated ion channels, and of membrane transporters as therapeutic agents. His group worked in a wide range of therapeutic areas including cardiovascular, CNS/pain, diabetes, immunology and inflammation, ophthalmics, and animal health. In 2009 Dr. Kaczorowski retired from Merck and established Kanalis Consulting, L.L.C. to continue working on drug discovery and development in the ion channel and transporter fields. He has over 200 peer reviewed publications, 15 issued patents and is on the Editorial Board of AJP. He also holds two Adjunct Professorships at University of Medicine and Dentistry of New Jersey and Robert Wood Johnson Medical School, and is a member of several scientific advisory boards.

Olaf Pongs graduated in Chemistry in 1967 and obtained his PhD in Biochemistry 1968. After postdoc years at Johns Hopkins University, Baltimore, the Max-Planck Institut for Molecular Genetics, Berlin, and the MRC Laboratory for Molecular Biology he has been appointed in 1976 full professor of Biochemistry at the Department of Chemistry of the Ruhr-University Bochum, Germany. In 1991 he became director of the institute for neural signal transduction at the Center for Molecular Neurobiology Hamburg (ZMNH). From 2004 until 2009 he was Head of the ZMNH. Since 2012 he is visiting professor at the institute of physiology, University Hospital of the Saarland. His main research interests encompass the structure of voltage-gated potassium channels in lipidic environments and aspects of their cardiac function and pharmacology. He is author of more than 300 full papers in internationally indexed journals and co-editor of several books. He has served as member of the editorial board of EMBO Journal, EMBO reports, and Channels, among others.

Ion channels play a fundamental role in cellular physiology and modulate a wide variety of cellular events throughout the body. In cardiovascular and renal systems, channels control electrical excitability, impulse conduction, muscle contraction, fluid secretion and other signal transduction processes, and, as such, they have been recognized as an important class of molecules for drug targeting. For example, small molecule modulators of ion channels have been used clinically as anti-arrhythmic, anti-hypertensive or diuretic agents for many years. Despite this success, there are still significant unmet medical needs in cardiovascular and renal medicine for which targeting ion channels may have therapeutic value. For example, sudden cardiac death precipitated by a lethal arrhythmia is a major medical issue. Such fatality might occur with otherwise normal, healthy people due to a genetic predisposition or in an impaired patient population due to acquired heart disease stemming from damaged cardiac muscle as a result of previous heart attack and/or congestive heart failure. Indeed, congestive heart failure is a major medical problem for which only limited therapies exist. In addition, atrial fibrillation, an arrhythmia with associated risk of stroke and heart failure, is another major unmet medical area which affects large numbers in industrialized societies, and whose population continues to grow with age and occurrence of structural heart disease. Even though hypertension is generally considered to be manageable by either single or combination drug therapies, there are still individuals who are refractory to current interventions, putting these people at risk for stroke and heart attack. Moreover, with the prevalence of type 2 diabetes increasing in industrialized nations, this situation coupled with the expanding incidence of obesity and metabolic syndrome, have produced a healthcare concern with a major cardiovascular element that is becoming of epidemic proportion.

In spite of these serious medical needs, it is somewhat paradoxical that Pharma has generally de-emphasized cardiovascular drug development in their portfolios, rather tending to focus on oncology, metabolic diseases and neural degeneration as more important therapeutic indications for prosecution. It is unlikely that this decision is driven by potential market size. Rather, it may reflect the prevalence of generic drugs that are available to treat well understood cardiovascular diseases, and to the large number of clinical failures that have occurred over the past 20 years (many of these with ion channel drug candidates) which focused on developing new therapies for conditions like arrhythmias. In terms of the latter, a retrospective analysis tends to indicate that those clinical failures were primarily due to poor target selection, to lack of drug efficacy because of poor physical chemical properties of development candidates (i.e., high protein binding limiting target engagement) and to low therapeutic index (i.e., ion channel poly-pharmacy

causing toxicity). For these reasons, in order to rejuvenate interest in cardiovascular drug development, new mechanisms with a higher probability of clinical success need to be identified for Pharma to regain interest in these highly relevant therapeutic areas. The purpose of this series of reviews is to illustrate such novel mechanisms, strategies and approaches which could support a new generation of drug discovery and development, potentially resulting in important breakthrough cardiovascular and renal therapies.

In the following commentary, we will discuss potential new therapeutic strategies for treating cardiac arrhythmias and hypertension. This effort is being complemented by recent advances in animal models of disease, high throughput screening for identifying drug lead structures, improvement in drug formulation approaches and development of effective paradigms to assess drug safety at the level of cardiovascular ion channels. In addition, important roles that personalized medicine and Human genetics can play in developing new cardiovascular therapies will be outlined, as well.

The cardiac Na channel (Nav1.5) has long been a target for treating cardiac arrhythmias, but previously developed drugs that block peak Na current are associated with increased mortality in Man. The manuscript by Remme and Wilde describes how new approaches that selectively block the late Na current, either directly at the level of Nav1.5, or indirectly by targeting Na1.5 regulation, might offer anti-arrhythmic activity with increased therapeutic index.

In the past, both Kv11.1 (hERG) and Kv7.1/minK (IKs) have been targets for treating ventricular arrhythmias because of the prominent role of each of these channels in mediating re-polarization of cardiac action potential. However, blockers of either channel type are known clinically to promote lethal arrhythmias. In a re-examination of this approach, Sanguinetti and Dvir *et al.* in their respective reviews, outline new ways in which each of these channels could still be targeted for therapy. For example, Kv11.1 agonists have potential use in treating pro-arrhythmic long QT syndrome, while understanding molecular properties of Kv7.1/mink mutations which are pro-arrhythmic is important for designing pharmacological strategies to appropriately treat such potentially lethal situations. Therefore, emphasis has shifted from broadly targeting these channels for therapeutic benefit, to correcting abnormalities in cardiac function resulting from mutations in these proteins.

Because of its specific distribution and presumed physiological role in the atria, Kv1.5 has long been considered a target for developing selective inhibitors to treat atrial arrhythmias, although no group has yet clinically achieved this goal, despite a very significant past and present effort. Plasticity in ion channel expression and electrical remodeling in diseased states constitute here a serious complication. The review by Wettwer and Terlau specifically addresses this issue and outlines need for new experimentation to clarify whether a path forward for pursuing Kv1.5 channel blockers to treat atrial fibrillation is feasible.

In addition to channels which directly control properties of atrial and ventricular cell action potentials, there are other channels in the heart, for example in the sinoatrial node and the Purkinje fibers, which control electrical conduction, cardiac rate and pacemaker activity. These channels may be targets for developing new anti-arrhythmic and/or bradycardic agents. Kruse and Pongs discuss the role of TRPM4, a member of the transient receptor potential ion channel family, in controlling cardiac rhythmicity, noting that mutations in this channel alter cardiac conduction which suggests ways of how direct pharmacological modulation may be therapeutic. Wahl-Schott *et al.* review the function of hyperpolarization-activated, cyclic nucleotide gated cation channels in SA nodal cells, providing a unified view of their many functions in this tissue. Targeting this channel may yield unique therapeutic benefits in terms of effecting cardiac rate control.

Although many *in vivo* animal models are used for investigating specific types of arrhythmias, unfortunately all of these are large species (e.g., dog, sheep, and monkey) which imposes serious limits on preclinical experimentation (i.e., expense, quantities of test compound required and regulatory issues). Therefore, small rodent animal models might be more useful, especially considering their utility when applying genetic approaches, than these other traditionally used species. Unfortunately, as Nerbonne relates in her review, mouse is limited for many such types of investigation because its cardiac physiology and cardiac ion channel complement (especially K channels) are markedly distinct from Man; thus, mouse does not recapitulate human cardiac physiology in many aspects. Yet, there are some similarities in pathophysiologies between the two species when certain channelopathies and Ca overload induced arrhythmias are considered, suggesting that mouse still can have utility based on the specific mechanism under investigation, and should be considered as an alternative investigative species when appropriate.

The review by Roden makes an important point that most arrhythmia drugs were developed when the mechanism(s) controlling these pathophysiologies were (and perhaps still are) poorly understood. Because of this notion, it is difficult to predict efficacy or toxicity of many anti-arrhythmic drugs with any certainty. With the advent of genetic typing of individuals that are prone to specific