INNOVATIVE DESIGNER NPS FOR CARDIORENAL DISEASE

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The earliest evidence describing the potential existence of the natriuretic peptide (NP) system and the concept of heart as an endocrine organ dates back to 1964 when Jamieson and Palade reported the presence of specific atrial granules in the heart and concluded that the atrial myocardium possesses a secretory function. Finally, a new era began in cardiovascular biology and therapeutics when, in 1981, de Bold *et al.* published the landmark study demonstrating that homogenates from the cardiac atria contained a potent diuretic and natriuretic peptide, establishing for first time the heart as endocrine organ. Shortly after, Flynn and de Bold from Canada and Kangawa and Matsuo from Japan reported almost simultaneously the complete amino acid sequence for the peptide that has come to be known as atrial natriuretic peptide (ANP), which has led to intensive research into the heart as an endocrine organ. Discovery of B-type natriuretic peptide (BNP) and then C-type natriuretic peptide followed the seminal discovery of DeBold over the following decade.

The natriuretic peptides today represent endogenous peptide molecules which are structurally similar yet genetically distinct that exert pleiotropic beneficial properties secondary to activation of their molecular targets which are particulate guanylyl cyclase (GC) receptors, resulting in generation of their second messenger, cyclic 3',5' guanosine monophosphate (cGMP). This family of peptides currently include ANP, BNP, CNP, *Dendroaspis* natriuretic peptide (DNP) and urodilatin. Most importantly, in

part, from the seminal work of the Nobel laureate Ferid Murad and colleagues, these peptides serve as potent endogenous particulate GC activators which, like nitric oxide, are powerful generators of cGMP. Furthermore, elegant gene disruption studies by David Garbers and Nobel laureate Oliver Smithies in murine models of altered NP production or disrupted GC receptors, clearly have established that these endogenous peptides play a fundamental role in cardiovascular homeostasis. The widespread expression of these GC receptors linked to the NPs and their physiological response to their activation establish the NPs as natriuretic, blood pressure lowering, renin and aldosterone suppressing, anti-hypertrophic, antifibrotic, lipolytic, lusitropic, endothelial regulating and angiogenic mediators. Such widespread biological actions make them highly attractive as therapeutic agents for a variety of diseases especially cardiovascular and renal disease. In this lecture, I will detail the NP/pGC/cGMP signalling pathway with a special emphasis upon the biological properties linked to all the NPs, noting that a human recombinant form of ANP, carperitide, has been approved in Japan for the treatment of acute decompensated heart failure (ADHF) since 1995, while a human recombinant form of BNP, nesiritide, has been approved for this same indication in the United States since 2001 and Canada since 2008. We will also highlight the therapeutics of the native NPs beyond ADHF and most importantly newer generation of designer NPs which are engineered based upon designs of native mammalian and non-mammalian NPs such as DNP isolated from the green mamba viper and possess novel properties which go beyond the native NPs.