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cGMP enhancing strategies for acute and chronic heart failure

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Acute and chronic heart failure (HF) are multi-organ and -cell syndromes characterized by myocardial structural and functional abnormalities, excessive vascular dysfunction and vasoconstriction, avid sodium retention, and neurohumoral maladaptations. In this syndrome, the cGMP pathway may be disrupted, either with impaired production of nitric oxide or its excessive degradation, thus impairing the soluble guanylate cyclase (sGC) signaling pathway or inadequate release of particulate guanylate cyclase (PGC) ligands such as the natriuretic peptide ANP or BNP or the release of abnormal forms, therefore impairing the PGC pathway.

We have explored in human and experimental HF novel therapeutic strategies targeting both acute and chronic HF in order to delay disease progression, improve myocardial and renal function and structure, and enhance clinical wellbeing.

In acute HF we have targeted SGC with a novel heme-independent and NO-independent molecule, BAY 58-2667. In acute congestive HF with marked decompensation, BAY 58-2667 improved myocardial function with a decrease in filling pressures both pre-load and after-load, with a preservation of renal function, consistent with enhancement of sGC/cGMP signaling. In contrast, we have designed and synthesized a novel PGC activator, which is CD-NP. This novel peptide possesses the 17-amino acid ring structure of CNP so as to target the NPR-B receptor but with the 15-amino acid C-terminus derived from DNP. This novel peptide, by targeting NPR-B, lacks hypotensive actions but decreases cardiac filling pressure through CNP/NPR-B venodilation, together with marked improvement in renal function, presumably due to the 15-amino acid C-terminus from DNP. Thus, these two cGMP activating molecules (BAY 58-2667 and CD-NP) have promise for the treatment of acute decompensated HF by targeting this important second messenger system.

So as to chronically enhance myocardial and renal function and structure in HF, we have recently completed studies employing a novel orally available conjugate of human BNP. By novel technology that makes this peptide orally available but preserves intrinsic cGMP activating properties, it emerges as a new generation of orally active peptitic molecules targeting cardiovascular disease. Recently published studies by our group demonstrate the ability in the conscious dog to absorb this novel conjugate to increase circulating levels of BNP, activate cGMP, and reduce arterial pressures. Studies are underway targeting both systolic and diastolic dysfunction in experimental chronic HF to improve myocardial and renal function and to reduce cardiac fibrosis, a hallmark of HF.