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EDITORIAL COMMENT

A Growth Tonic for Heart Failure?*

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The mammalian heart is under constant and unavoidable assault from oxidant stress. Many of these oxidant stressors are the byproduct of normal functioning of the heart, given its large factories of mitochondria. Unlike epithelial cells, which are also highly exposed to environmental stress, cardiac myocytes cannot be easily sloughed and replaced when damaged. Accordingly, myocardial cells are equipped with a number of powerful damage-protective strategies, including oxidant buffers and survival factors that ward off premature cell death decisions in the face of temporary challenges. When these protective mechanisms are impaired, the heart becomes more vulnerable to a range of toxic and oxidative stresses.

Neuregulin-1 is part of a family of naturally occurring membrane-anchored or secreted glycopeptides related to epidermal growth factor (EGF) that have multiple effects on the nervous and cardioldelim vascular systems (1,2). Neuregulin was originally thought to be a ligand for the EGF receptor (EGFR) Neu (HER2, ErbB2), and its name reflects that history; it is now known to bind 2 other EGFRs, ErbB3 and ErbB4. Neuregulin-1 binding leads to the preferential formation of ErbB2- ErbB4 heterodimers, activation of ErbB receptor tyrosine kinase activity, and downstream signaling through phosphotidyl inositol 3-kinase and Akt.

Neuregulin is secreted by epithelial cells that lie in close proximity to myocytes, as in endocardial and microvascular epithelia, and exerts paracrine effects on myocytes that pattern normal cardiac development, and control myocyte proliferation and differentiation (3). Genetic deletion of neuregulin or its receptor ErbB4 confer similar defects in heart development and lead to early embryonic lethality (2).

In the adult heart, neuregulin is activated by stress (4) and has a number of actions that are potentially favorable to cardiac function and repair after injury. Notably, neuregulin has been shown to promote generation of new myocytes during development, and for a short window of time after birth in injury models (5-7). Application of neuregulin to myocytes from older animals has little effect on proliferation, possibly due to the downregulation of both ErbB2 and Erb4 on these cells after birth (5,6,8). Neuregulin can also promote the emergence of mature cardiomyocytes from progenitor cells (9-11), improve contractility and glucose uptake (12), and favorably alter the balance of adrenergic and cholinergic tone in the myocardium (1). Importantly, it appears to protect against cell loss during oxidative stress in both small and large animal models (13-15).

The importance of neuregulin signaling in the heart came to wide attention in the late 1990s, when inhibitors of HER2/Neu/ErbB2 became available for the treatment of breast cancer. A significant subset of breast cancers over-express ErbB2, leading to ligand-independent activation of its strong pro-growth signal. Women receiving trastuzumab, a monoclonal antibody against ErbB2, developed significant cardiotoxicity, particularly if they were also receiving anthracyclines. These observations confirmed in humans the essential role for neuregulin signaling in maintaining cardiac homeostasis during normal function and stress (16).

Cimaglermin alfa is a recombinant human protein derived from the neuregulin-1 gene. Preclinical studies have provided strong support for its efficacy in preserving and improving cardiac contractile function, and in defending the heart and other tissues against stress. In a rat stroke model, treatment with cimaglermin initiated as late as 7 days after permanent middle cerebral artery occlusion promoted signs of molecular and functional recovery, without affecting the size of the infarction (17).

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In this issue of *JACC: Basic to Translational Science*, Lenihan et al. (18) report the results of a first-in-human phase 1b trial of the effects of cimaglermin alfa in patients with patients with heart failure and reduced ejection fraction (HF-REF). The trial was rigorously designed as a double-blind, placebo-controlled study of a single 20-min intravenous infusion of cimaglermin in 7 ascending dose cohorts. Enrollment was terminated by the appearance of adverse effects in the highest dose cohort. Of a total of 40 subjects, 27 were randomized to cimaglermin and 13 patients to placebo. All patients had left ventricular ejection fractions (LVEFs) <40%, and all had previously implanted converter-defibrillators. Safety determinations included standard electrocardiographic and clinical laboratory tests; in addition, echocardiographic measurements of left ventricular function were obtained at assessment visits up to 12 weeks after treatment.

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The key finding is that pooled data from the high-dose cohorts (who received between 0.189 mg/kg and 1.5 mg/kg) compared with placebo shows a significant increase in LVEF of roughly 8% at 30 days after infusion; this increase was sustained 3 months later. When the limiting 1.5-mg/kg dose (n = 3) is excluded, the increase at 90 days is not statistically significant, but the 30-day response remains. The results are intriguing, and congruent with a previous study of a peptide derived from the receptor-activating domain of neuregulin (19), in which safety and a trend towards increased LVEF were reported. Notably, all 22 patients who received cimaglermin in the trial have completed a planned year of follow-up this July, and further information will likely be forthcoming in the new year.

There is a relative dearth of truly novel approaches to heart failure, especially treatments that target the myocyte itself rather than its hemodynamic demands. Hence, the attractiveness of a therapy that may act directly on myocyte cell fate decisions, similar to the recent enthusiasm for regenerative therapies in heart failure. Especially given the desperate lack of alternatives for this crippling and ultimately fatal disease and the many years of dedicated effort by this research team, the opportunities for positive bias are many. There are significant weaknesses to the current study. The small number of subjects, the even smaller number of patients in the responding group, the weakness of the experimental endpoint (echocardiographically determined LVEF), and the biological implausibility of an enduring treatment effect of a brief 1-time drug infusion, warrant an excess of caution.

Efficacy, even if borne out by future studies, is only part of the problem. Completion of the phase 1b trial reported here was delayed for a time by the appearance of transient hepatotoxicity (elevated alanine aminotransferase, aspartate aminotransferase, and bilirubin) in 1 patient who received the study drug and another who had been reported as part of a previous phase 1 trial. In both cases, the subjects were asymptomatic, and the biochemical abnormalities resolved spontaneously after several days. Whether this, or other toxicities yet to be identified during larger trials, represents a significant limitation to further progress in the clinic is impossible to determine at this point. The safety and tolerability of a drug for heart failure depends a great deal on the dosing schedule, as well as the impact of the drug on survival, hospitalization rates, symptoms, and requirements for other interventions, including implantable devices. Some symptoms may be acceptable if the drug is given as a monthly infusion, but completely unacceptable as part of a daily regimen.

Similarly, concerns about the promotion of cancer by cimaglermin are unlikely to be assuaged by the small trial presented here. Although neuregulin is unlikely to be a tumor driver in the absence of ErbB2 upregulation, it is possible that it could assist in bypassing ErbB2 inhibitors, which upregulate ErbB3 expression and could promote the formation of new oncogenic dimers with ErbB2 (20). Choice of patient, timing, and dose schedule will have important and as-yet-undetermined effects on that risk.

Yet optimism is still appropriate, given these early results. It is a given that progress in the treatment of heart failure requires a high tolerance for risk. Many exciting basic science concepts have met disappointment on the path to translation. At the same time, too much skepticism can smother good ideas in the cradle, and paradigm-shifting treatments cannot be recognized until conceptual resistance has had a chance to be overcome by strong data. The editors of *JACC Basic to Translational Science* are pleased to provide a forum for innovative first-in-human studies, especially when they are backed by solid basic science, extensive preclinical data, and a rigorous study design. All of these are fully in evidence in this provocative and potentially important paper. (A Double-Blind Pharmacokinetic Interaction Study Evaluating the Effect of a Single IV Infusion of GGF2 or Placebo on Midazolam Pharmacokinetics in Patients With Heart Failure; NCT01944683).

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