A bench-to-bedside story

Canada Research Chair in Experimental Cardiology, Professor Morris Karmazyn discusses his novel investigations into the cardiac benefits of sodium-hydrogen exchange inhibition, and his exciting hopes and predictions for the promising future of heart failure research.

On a personal level, what drew you to the study of cardiology and, more specifically, cardiac protection against myocardial ischaemia and reperfusion?

My mother’s death from rheumatic heart disease at a relatively young age was certainly an impetus for my early interest in cardiac research; although my progression to the specific area of cardioprotection arose later when, as a junior faculty member, we tested the concept of sodium-hydrogen exchange (NHE) inhibition as a promising therapeutic target. The vast majority of our studies dealing with ischaemia and reperfusion over many years were indeed almost exclusively related to NHE, as we saw substantial clinical potential in this.

Could you explain the role of NHE and why your laboratory chose to focus on this mechanism?

NHE is a family of membrane-bound proteins consisting of at least 10 distinct isoforms, designated NHE-1 to NHE-10. Their function is to transport sodium and hydrogen ions in opposite directions. Some of these isoforms are expressed in distinct organs or intracellular organelles, so they can be quite specific in their localisation and function. The NHE-1 isoform is ubiquitously expressed in most tissues, and is the predominant type found in the cardiac cell. It extrudes protons during acidosis, and therefore its activity is stimulated during ischaemia. Because sodium ions enter while protons are removed, a sodium-dependent calcium overload occurs, and this leads to cell death. Clinical development of NHE inhibitors has thus focused on targeting the NHE-1 isoform.

The decision to pursue NHE-related research was not due to any conceptual insights on my part or a Eureka moment. Instead, my late wife, Dr Margaret Moffat, a cardiac electrophysiologist and visionary with outstanding scientific insights, suggested to me that I study this exchanger – ironic actually, as electrophysiologists generally do not study NHE since it is an electroneutral system!

As the first to show that inhibiting NHE pharmacologically protects the heart against ischaemic injury, what were the consequences of your laboratory’s revelation?

Unbeknownst to me, a number of pharmaceutical companies were considering the concept of NHE inhibition as a cardioprotective strategy around the same time that our initial paper was published. I subsequently learned from discussion with industry colleagues that the decision to pursue this avenue of drug development was propelled by the publication of our early results. That was certainly rewarding, as was the relatively rapid development of these drugs for clinical trials. It is a true bench-to-bedside story.

Can you discuss the progress you have made since your research on NHE began?

Our initial findings on NHE and cardiac protection were initially greeted with some degree of scepticism. It was therefore heartening to see that our 1988 report was rapidly followed by a large number of studies showing the efficacy of NHE inhibition as a cardioprotective strategy. This was aided in no small part by the development of very specific NHE-1 inhibitors by the pharmaceutical industry. Having our original finding translate to clinical studies was certainly exciting, but at the same time frustrating in view of mixed outcomes. Our major change in direction was to expand this work to the heart failure area, where we have achieved very promising results.

What are your hopes for the future of heart failure treatment strategies?

I am an optimist at heart (no pun intended) and these are exciting times for heart failure research, with outstanding work being carried out by many laboratories around the globe. I am not sure if a cure is within our grasp in the foreseeable future but improved management is certainly feasible. An analogy with HIV/AIDS may be germane; although there is still no cure, life expectancy for AIDS patients has increased tremendously because of the development of multidrug antiretroviral ‘cocktails’. In fact, many consider AIDS today as a chronic, but not necessarily fatal condition. I believe an effective heart failure cocktail encompassing the most promising drugs, each targeting distinct pathological processes, is within reach and is critical for managing such a complex syndrome.
Heart at work

Research conducted in the Department of Physiology and Pharmacology at the University of Western Ontario, Canada, explores the underlying mechanisms of heart failure. The aim is to develop innovative strategies for reducing the severity of heart failure and improving survival.

Heart Failure is the consequence of myriad molecular, biochemical and cellular processes and represents a major health threat in Canada. To date, more than 550,000 Canadians are living with heart failure which carries a five-year survival rate of 50 per cent, and incidence has almost doubled in recent years. Moreover, survivors often experience emotional, physical and financial strain and thus a burdensome quality of life.

Though the pathology of a malfunctioning heart is commonly associated with the organ’s inability to efficiently pump blood, there is an array of potential causative factors, making heart failure a challenging condition to treat. Researchers are currently studying a variety of approaches to develop new treatment strategies for heart failure patients. One such researcher is Professor Morris Karmazyn, Canada Research Chair in Experimental Cardiology, whose work is unravelling the mechanisms involved in the condition, taking a rather eclectic approach to investigating the possibility of treating heart failure using a combination of pharmaceutical and alternative methods. His laboratory’s untraditional approach was borne from the understanding that disease, as an often complex enigma, is most effectively explored from multiple angles within the medical field.

Cardioprotection

Karmazyn has focused much of his earlier research on cardioprotection, and in 1988 the Karmazyn Laboratory at Dalhousie University, Nova Scotia, Canada, was the first to identify that the pharmacological inhibition of a membrane-bound protein, sodium-hydrogen exchange (NHE) protects the heart against ischaemic injury. This discovery was followed by research that demonstrated that this heart cell acidity regulator plays a key role in damaging the heart during ischaemia as well as the deterioration of cardiac function, which led the laboratory to translate their research for the eventual development of highly specific NHE inhibitors for clinical trials. The challenge associated with previous cardioprotection research was the frequent miscorrelation between positive experimental trials and unsuccessful clinical trials. The failure of the cardioprotection clinical trials, despite encouraging results during experimentation with animal models, is likely due to the heterogeneity of patient populations, particularly in terms of age and comorbidities. Animal models tend to be young and healthy, and are thus neither truly representative of human age nor cardiac function. Practical elements also affect the outcome of the trials; though experimental studies have shown optimal effectiveness of drug administration before the onset of ischaemia, this is extremely difficult to replicate in a clinical setting.

Following a series of NHE inhibitor trials, the last and most significant was the EXPEDITION study, the results of which were published in 2008. Despite unearthing the first ever positive results of myocardial protection in a clinical setting, the side effects of the NHE-1 isoform specific inhibitor cariporide included a significantly higher incidence of stroke; negating the possibility of its use for cardiac patients. However, the exact link between cariporide and the onset of stroke remains unclear: “This is unfortunate as NHE-1 inhibition likely offers a very attractive opportunity for cardiac therapeutics,” Karmazyn emphasises.

Heart Failure Treatment

Subsequent to their NHE research for cardioprotection, Karmazyn’s group is investigating myocardial remodelling, an underlying factor that contributes to the development of heart failure. The process takes place post-injury over time, weakening the organ. Ventricular hypertrophy is a key component of myocardial remodelling, manifesting itself as an abnormal and excessive growth of the heart muscle and compromising cardiac function. Over the last 14 years, the lab has focused on an exploration of hypertrophy with the aim of developing a solution to prevent, and most importantly reverse, the process. The signalling pathways involved in hypertrophy are complex, so if better understood, much needed therapeutics could be developed for heart failure patients.

Combining hypertrophy research with his studies on NHE, Karmazyn was the first to show that NHE inhibition is an effective method of reducing experimental heart failure, demonstrating that NHE impacts the heart because it functions upstream of key cell signalling prohypertrophic factors. The group identified that NHE inhibition reduces calcineurin activity caused by increased calcium levels, which provokes hypertrophy. Thus, their study of myocardial remodelling represents a considerable step toward a more thorough understanding of the mechanisms of heart failure, enabling the eventual development of effective therapeutics.

Obesity and Heart Disease

Since his study on NHE began, Karmazyn’s research has evolved considerably and now includes an investigation of the role of the protein leptin in obesity-related heart disease. First discovered in 1994 by Jeffrey Friedman and his research group at Rockefeller University, USA, leptin is a protein belonging to the adipokines family. At the time, this finding was met with considerable interest amid scientists and the general public, as leptin primarily functions as an appetite suppressant that directly signals the brain. Despite initially sparking interest as a potential obesity treatment, research soon demonstrated that leptin could not be translated into an effective pharmaceutical intervention.

The discovery of leptin has nevertheless assisted the field of adipobiology – the study of adipokines and their implication in the pathogenesis of obesity and related cardiometabolic disease. Many adipokines such as leptin are produced by tissues other than adipocytes, including the heart. Identifying receptors for leptin in heart cells suggests that the protein exerts biological effects upon the organ. Karmazyn and his research group were the first to demonstrate the prohypertrophic effect of leptin, which signals the heart to increase in size. A central signalling process is the Ras homologue A (RhoA)/Rho-associated protein kinase (ROCK) signalling pathway, which is activated by the protein and is implicated in the coordination of these key prohypertrophic mechanisms.

Keeping his research in the adipokines family, Karmazyn is investigating the interaction between different proteins, as contrary to leptin, adiponectin has a beneficial impact on the heart. To date, numerous clinical trials have identified that the ratio of adiponectin to leptin plasma concentrations could accurately pinpoint the contribution of these adipokines to cardiovascular disease.

Natural Products

In addition to the study of proteins and their effects on cardiac function, Karmazyn’s laboratory has been researching the impact of natural products on the heart. To date, the researchers have identified the possibility of using ginseng – a holistic medicine that has been used in Asian societies for thousands of years – to counteract heart failure. During test phase, the plant extract proved an effective antihypertrophic agent capable of preventing and reversing experimental heart failure. More extensive studies are underway with a view to better understanding the underlying mechanisms responsible for ginseng’s beneficial
effect on the heart. The challenge with pinpointing the mechanistic benefits of ginseng arises from the dozens of bioactive compounds found in the plant, any of which could be the source of this natural form of cardioprotection. As an inexpensive and widely-available extract, ginseng could open new pathways to overcome the inability of pharmaceuticals to reverse cardiac hypertrophy or heart failure.

In collaboration with investigators at the Canadian Research and Development Centre for Probiotics, the group is also exploring the use of probiotics for cardiac treatment. Most commonly associated with gastrointestinal health, Karmazyn’s lab has demonstrated that these natural bioactive compounds have the ability to slow the pathogenesis of heart failure in animal models. Though the mechanism of these natural products is yet to be fully understood, they could represent effective future treatments for heart failure, especially in conjunction with pharmaceutical therapies.

Despite the unwanted side effects, having proven that NHE-1 inhibition is cardioprotective, the EXPEDITION study has paved the way for further exciting discoveries, leading to more expansive research on cardiac malfunction that may hold the key to better understanding and treating the heart.

**KEY SUCCESSES IN THE KARMAZYN LAB**

- Sodium hydrogen exchange as a target for cardioprotection
- Sodium hydrogen exchange inhibition for treating heart failure
- Leptin and cardiac hypertrophy
- Research into natural products and heart failure

**HYPERTROPHIC SIGNALS**

NHE-1 PATHWAY IN HYPERTROPHY

- H⁺
- 3Na⁺
- Na⁺
- Ca²⁺
- NHE-1
- NCX
- Transcription ← NFAT
- NFAT dephosphorylation
- Other calcium dependent effects
- Calcineurin activation

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