## FAST BREAKING PAPERS - 2008

### December 2008

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**Peter Ferdinandy talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper in the field of Pharmacology & Toxicology.**

**Article Title: Interaction of cardiovascular risk factors with myocardial ischemia/reperfusion injury, preconditioning, and postconditioning**
Authors: Ferdinandy, P;Schulz, R;Baxter, GF
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* Univ Szeged, Dept Biochem, Cardiovasc Res Grp, Pharmahungary Grp, Domter 9, H-6720 Szeged, Hungary.
* Univ Szeged, Dept Biochem, Cardiovasc Res Grp, Pharmahungary Grp, H-6720 Szeged, Hungary.
(addresses have been truncated)

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**SW: Why do you think your paper is highly cited?**

Our paper provided a new aspect of a more than 20-year-old research field, i.e., the endogenous stress adaptation of the myocardium.

**SW: Does it describe a new discovery, methodology, or synthesis of knowledge?**

Our review paper describes a synthesis of knowledge which accumulated over the past decade and highlights a clinically very important, novel aspect of the field, which was neglected by most of the opinion leaders for many years. We are very happy that the paper is now highly cited. It was a long way to go, but we are certain that our approach to this scientific field will be recognized by scientists and the pharmaceutical/biotech industry quite soon.

**SW: Would you summarize the significance of your paper in layman's terms?**

Ischemic heart disease (i.e., insufficient blood flow in the heart muscle leading to myocardial infarction and heart failure) is the leading cause of death in the industrialized world. The treatment of acute ischemic heart disease has entered a new era where mortality can be approximately halved by procedures which allow the rapid return of blood flow to the ischemic zone of the myocardium, i.e., "reperfusion." Reperfusion, however, may lead to further complications such as diminished cardiac contractile function and arrhythmia.

Earlier pharmacological approaches to attenuate the consequences of ischemia/reperfusion injury have been of limited experimental efficacy or have failed to translate into useful clinical treatments. However, the heart has been shown to possess a remarkable ability to adapt to ischemia/reperfusion stress and it has

been the focus of intense research.

"Ischemic preconditioning" is a well-described adaptive response in which brief exposure to ischemia markedly enhances the ability of the heart to withstand a subsequent ischemic injury. Moreover, brief cycles of ischemia/reperfusion applied following a longer period of ischemia also confer cardioprotection against the consequences of myocardial ischemia/reperfusion, a phenomenon called "ischemic postconditioning." The discovery of these two major forms of endogenous cardioprotective mechanisms has encouraged the exploration of new ways to protect the ischemic/reperfused myocardium, but still has not led to a translation into clinical therapies.

Most experimental studies on cardioprotection have been undertaken in animal models, in which ischemia/reperfusion is imposed in the absence of other disease processes. However, ischemic heart disease in humans is a complex disorder caused by or associated with known cardiovascular risk factors, including hypertension, hyperlipidemia, diabetes, insulin resistance, atherosclerosis, and heart failure; additionally, aging is an important modifying condition. In these diseases and aging, the pathological processes are associated with fundamental molecular alterations that can potentially affect the development of ischemia/reperfusion injury and adaptation processes per se and responses to cardioprotective interventions.

The aim of our review was to show the potential for developing cardioprotective drugs based on endogenous cardiac stress adaptation and to review the evidence that comorbidities and aging accompanying ischemic heart disease modify responses to ischemia/reperfusion and the cardioprotection conferred by preconditioning and postconditioning.

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We emphasized the critical need for more detailed and mechanistic preclinical studies that examine cardioprotection, specifically in relation to complicating disease states. These are now essential to maximize the likelihood of successfully developing rational approaches to therapeutic protection for the majority of patients with ischemic heart disease who are aged and/or have modifying comorbid conditions.

**SW: How did you become involved in this research, and were there any problems along the way?**

I was inspired by the late Dr. Matyas Koltai of L'Institut Henri Beaufour, Le Plessis Robinson, France, and Dr. Arpad Tosaki of the Department of Pharmacology, Szeged Medical University, my mentors who introduced me into cardiovascular research in the early '90s. At that time, research on ischemic preconditioning was very new and hot. During the years 1995 through 1997, we had first shown that endogenous cardiac adaptation in hypercholesterolemic and in nitrate-tolerant animals was not as effective as in healthy animals. We knew that these were very important findings but surprisingly, very few research groups got involved in this line of research.

In 1998, we published a review which highlighted that preconditioning could be a phenomenon that works only in healthy experimental animals, but we had received very few citations. However, we continued to do follow-up on this line and identified some cardioprotective pathways that are disrupted in the presence of hyperlipidemia. In the meantime, we realized that more and more research groups were becoming interested in this field. I realized, in 2007, that the time was right to write an extensive review in a high-ranking journal in order to increase interest in this filed, and, in 2009, our review published in *Pharmacological Reviews* has been selected as a "Fast Breaking Paper" by *ScienceWatch.com* from Thomson Reuters.

**SW: Where do you see your research leading in the future?**

As a scientist, my research group shall continue exploring the disruption of cardioprotective signaling pathways in the presence of hyperlimidemia and diabetes and identifying new therapeutic targets for potential drug development. As an entrepreneur, PharmaHungary™ will develop new animal models for preclinical pharmacology services and develop drugs that protect the ischemic myocardium even in the presence of hyperlipidemia or metabolic diseases such as diabetes. And this is where I see our research leading, toward the identification of new drug targets and the development of new cytoprotective drugs which are effective against ischemic heart (and other organs) disease, even in the presence of major cardiovascular risk factors.

**SW: Do you foresee any social or political implications for your research?**

If research on cardiac stress adaptation will follow the direction which we have highlighted in this paper, more efficient drugs will be developed to prevent and to treat ischemic heart disease, including myocardial infarction, and the success rate of drug development in this field will definitely be increased.

**Peter Ferdinandy, M.D., Ph.D., M.B.A.**
**Professor of Biochemistry and Clinical Pharmacology**
**Cardiovascular Research Group (cardiovasc™)**
**Department of Biochemistry**
**University of Szeged**
**Szeged, Hungary**
**and**
**Chief Executive Officer**
**PharmaHungary™ Group**
**Szeged, Hungary**
**Web ¦ Web**

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