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TRACKING TRENDS & PERFORMANCE IN BASIC RESEARCH



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2008 : September 2008 - New Hot Papers : Robert J. Lefkowitz

**NEW HOT PAPERS - 2008**
**September 2008**


**Robert J. Lefkowitz talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Biology & Biochemistry.**


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**Article Title: beta-arrestins and cell signaling**

Authors: DeWire, SM;Ahn, S;Lefkowitz, RJ;Shenoy, SK

Journal: ANNU REV PHYSIOL

Volume: 69

Issue:

Page: :483-510

Year: 2007

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

The discovery that beta-arrestins could serve as signaling molecules in their own right, in addition to their classical desensitizing functions, changed the paradigm for understanding how G protein-coupled receptors signal and are regulated. The field has grown rapidly over the past 10 years. This review article summarized and synthesized developments in this field with an emphasis on recent papers demonstrating how the newly discovered signaling pathways regulated physiology *in vivo*.

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

The paper summarizes and synthesizes knowledge in a rapidly expanding field of research, namely that of beta-arrestin mediated signaling.

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

Receptors are molecules on or in cells which bind to drugs and hormones, thus allowing them to initiate their effects on cellular physiology. The largest class of receptors is called G protein-coupled receptors. This large family of receptors containing almost a thousand members contains receptors for such commonly used drugs as "beta blockers," angiotensin receptor blockers (ARBs), antihistamines, and anti-platelet drugs such as clopidogrel, to name but a few.

The receptors are termed G protein-coupled receptors (GPCRs), because their actions have been thought for many years to be mediated solely through a type of protein called G proteins. Several years ago we discovered that there was an entirely different mechanism by which the receptors could work by using a

molecule called beta-arrestin, which we had previously discovered because it actually turns off G protein-mediated signaling.

This discovery has led to a completely new understanding or paradigm for how the receptors work, which has important implications for drug discovery. This is important because GPCRs are the most important target of therapeutic drugs.

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

This is a very long story because we discovered the beta arrestins 15-20 years ago. We discovered them as molecules which turned off or desensitized G protein-mediated signaling by the receptors. It was about 10 years later that we discovered their ability to actually serve as signaling molecules in their own right.

As with most new ideas, initially there did not seem to be great enthusiasm for this discovery. However, in recent years it has been widely accepted and now there are hundreds of papers on the subject. It is very difficult to change a scientific paradigm once it is well established.

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

At a basic science level, I think that research in this field will lead to a much deeper understanding of how the receptors work and are regulated. Whole new pathways and networks will be uncovered which are activated through the beta-arrestin molecules.

I think we have just scratched the surface in terms of their various functions. Another very important ramification of the work will hopefully come from the development of novel drugs, which are able to specifically target these newly discovered pathways leading to novel therapeutic effects and perhaps more limited side effects.

**Robert J. Lefkowitz, M.D.**  
**James B. Duke Professor of Medicine**  
**Investigator, Howard Hughes Medical Institute**  
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**Durham, NC, USA**

Keywords: beta-arrestins, G protein-coupled receptors, G protein-mediated signaling, beta-arrestin mediated signaling, beta-arrestin molecules, beta blockers, angiotensin receptor blockers, antihistamines, anti-platelet drugs.



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