

Electrophysiological Methods to Classify Drugs

Application

- ◆ *More efficient drug discovery*
- ◆ *Method to classify drugs against G-protein*
- ◆ *Cystic fibrosis as a first indication*

Advantages

- ◆ *Alternative methods are needed to classify ligands for Gs-protein coupled receptors*

Introduction

We have discovered a new method to classify ligands for G-protein coupled receptors as full agonists, partial agonists, neutral antagonists, or inverse agonists that do not have the disadvantages of the methods currently used to classify Gs-protein coupled receptor ligands.

Existing methods have numerous drawbacks and disadvantages. Some require the use of radioisotopes and/or indirect measure receptor-ligand interactions, examining events that occur several steps downstream of the signal transduction cascade. As a result, the responses measured are sometimes artificially amplified, concluding in a higher incidence of false positives. Artificially amplified responses also make it difficult to distinguish full agonists from partial agonists and neutral antagonists from inverse agonists.

Our invention compliments existing methods including:

- * Functionally classify ligands that interact with G-protein coupled receptors involves measurement of activity at the G-protein level, most typically GTPS binding and GTPase activity.
- * Testing for downstream activity in the G-protein coupled receptor signaling pathway. Specific examples include measuring cyclic adenosine monophosphate (cAMP) accumulation or protein kinase A activation, using techniques that include cystic fibrosis transmembrane conductance regulator (CFTR) channel activation, radioimmunoassay, and fluorescence measurements.

CONTACT



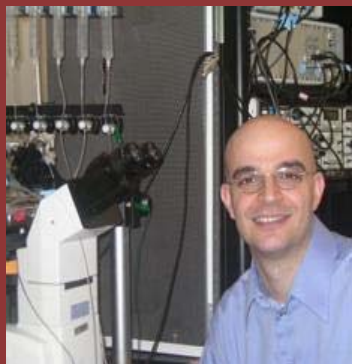
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About the Inventor

Tooraj Mirshahi, PhD is a Staff Scientist at the Weis Center for Research. Dr. Mirshahi received his PhD from Virginia Commonwealth University, graduating in 1997 and completed his postdoctoral training at Mount Sinai School of Medicine from 1997 to 2004.

Selected publications includes:

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3. Zhang H., Craciun L.C., Mirshahi T., Rohacs T., Lopes C.M.B. and Logothetis D.E. (2003) PIP₂ activates KCNQ channels and its hydrolysis underlies receptor-mediated inhibition of M currents. *Neuron* 37, 963-975
4. Jin, T., Peng, L., Mirshahi, T., Rohacs, T., Subunits of G Chan, K.W., Sanchez, R., and Logothetis, D.E. (2002). The $\beta\gamma$ Proteins Gate a K⁺ Channel by Pivoted Bending of a Transmembrane Segment. *Mol. Cell* 10, 469-481.
5. Mirshahi, T., Mittal, V., Zhang, H., Linder, M.E., and Logothetis, D.E. (2002a). Distinct Sites on G Protein $\beta\gamma$ Subunits Regulate Different Effector Functions. *J Biol. Chem.* 277, 36345-36350.
6. Mirshahi, T., Robillard, L., Zhang, H., Hebert, T.E., and Logothetis, D.E. (2002b). G β Residues That Do Not Interact with G α Underlie Agonist-independent Activity of K⁺ Channels. *J Biol Chem* 277, 7348-7355.
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