Isaiah T Arkin, J Antivir Antiretrovir 2011, 3:4
doi: http://dx.doi.org/10.4172/1948-5964.S1.8

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
VIROLOGY
5-7 September 2011 Baltimore, USA

How do aminoadamantanes block the influenza M2 channel and how does resistance develop?

Isaiah T Arkin

The Hebrew University of Jerusalem, Israel

The interactions between channels and their connate blockers are at the heart of numerous biomedical phenomena. Herein, we unravel one particularly important example bearing direct pharmaceutical relevance: the blockage mechanism of the influenza M2 channel by the anti-flu amino-adamantyls (amantadine and rimantadine) and how the channel, and consequently the virus develop resistance against them. Using both computational analyses and experimental verification, we find that amino-adamantyls inhibit M2's H+ channel activity by electrostatic hindrance due to their positively charged amino group. In contrast, the hydrophobic adamantyl moiety on its own, does not impact conductivity. Additionally, we were able to uncover how mutations in M2 are capable of retaining drug binding on the one hand, yet render the protein, and the mutated virus, resistant to amino-adamantyls, on the other hand. We show, that the mutated, drug resistant protein has a larger binding pocket for the drug. Hence, despite binding the channel, the drug remains sufficiently mobile so as not to exert a H+-blocking positive electrostatic hindrance. Such insight into the blocking mechanism of amino-adamantyls, and resistance thereof, may aid in the design of next generation anti-flu agents.

Biography

Isaiah T Arkin obtained his Ph.D at the age of 30 years from Yale University. He served for several years on the faculty of Cambridge University, department of biochemistry, after which he joined the Hebrew University of Jerusalem. At the Hebrew university he served as head of the life sciences institute and he is now the vice president for Research and development of the entire university. He has published more than 75 papers in reputed journals and is a recognized world leader in the field of viral ion channels.