Decoding the signals: Conversation with Dr. Rony Seger

Disease Biology: First of all on behalf of whole Disease Biology team and our readers, I welcome you on Disease Biology and thanks for giving us your precious time for this interview. As a biologist, you are not bound to an introduction, but as a part of formality, would you like to tell us a little bit about yourself to our readers?

Dr. Seger: I am a professor and head of the department of Biological Regulation, the Weizmann Institute of Science, Rehovot, Israel. I completed a BSc degree in Biology at Ben Gurion University (Beer Sheva, Israel) and then MSc and PhD in the Weizmann Institute of Science (Rehovot Israel). Upon completion of my doctorate with the late Prof. Shmuel Shaltiel in 1989, I joined the group of the late Prof. Edwin G. Krebs, Nobel Price Laureate at the University of Washington, Seattle, as a post-doctoral fellow. In this group Iparticipated in the identification of the MAPK/ERK cascade, by identifying and cloning MEK1. I am married to Dalia, and have two children.

Disease Biology: Please tell us something about your research.

Dr. Seger: I am continuing to work in the field of MAPK signaling and my findings in the last 20 years include: 1) Development of the first anti phospho antibodies for the study of MAPK activity;

2) Identification and study of the role of alternatively spliced isoforms of ERK1/2;

3) Elucidation of mechanisms that govern the subcellular localization of MAPK components, in particular their mechanism of nuclear translocation;

4) Establishing the use of nuclear translocation of MAPK as a therapeutic target for cancer;

5) Identification of new substrates and interacting proteins of MEK1/2 and ERK1/2.

My group is also interested in the study of anti-angiogenesis, regulation of dephosphorylation of various intracellular signaling components and effect of non-ionizing radiation on MAPK signaling. Ihave published over 200 papers in leading journals, and supervised more than 70 research students and post-doctoral fellows

Disease Biology: What prompted/inspired you to come to biology and to focus on cellular signaling for your research?

Dr. Seger: During my PhD studies, I worked on protein degradation, and studied the role of the Proteinase Meprin in regulating membranal receptors (e.g. EGF and Insulin receptors). When I moved to Seattle for a postdoctoral training, I decided to look at the mechanism by which these receptors transmit their signals al the way from the plasma membrane to the cell nucleus, which was at that time (Late 1980's) an open question in the field.

Disease Biology: In this journey a lot of moments would have come which gave you lessons, some would have been good, some would have been not so good. Would you like to share any memorable incident of your life as a researcher?

Dr. Seger: Indeed, I had many "high" and "low" moments throughout the past 30 years. The main highlights are usually new finding that provide breakthrough information on important biological questions. I still remember the excitement when we found the involvement of Importin7 in ERK1/2 translocation, and their way to inhibit nuclear translocation of the kinases. Obviously, other memorable moments have to do with the acceptance of papers by good journals or the success of grant applications.

Disease Biology: In your opinion, what are the lacks in current research in your field?

Dr. Seger: One point that is not well understood is the mechanism by which signaling molecules translocate into the nucleus upon stimulation. Interestingly, exposure of cells to various ligands and environmental cues results in a rapid (5-15 min) and massive (up to 10^8 molecules) nuclear translocation of a large number of proteins. This translocation serves as an unexplored layer of transcriptional regulation, and therefore, it is very important to study its nature. As of today, it is clear that most of these proteins are using neither the canonical nuclear localization signals (NLS), nor the well-studied Importin □□□ for this translocation, and the mechanism used here is largely unknown. In the past years we found that unlike Importin □□□ ,the group of□-like importins translocate to the nucleus upon stimulation, and we suggest that these proteins may be the main mediator of the stimulated translocation. However, at this stage

very little is known about their structure, function and mechanisms, and it would be great if more researchers would enter the field to provide more information on this important process.

Disease Biology: How you like to see your discoveries to be implemented to clinics?

Dr. Seger: Recently we provided a proof of principle for the use of nuclear translocation as a drug target for cancer and inflammation. I truly hope that "translocation-inhibitors" will be developed as treatment for various diseases including: cancer, autoimmune diseases, neurological disorders and others.

Disease Biology: we are all aware of the fact now that cancer is becoming a more severe due to the fact that drug resistance is appearing as a hindrance evil. So what do you think about personalized medicine for cancer patients in this regard? How far is there any approach for this personalized medicine and how much helpful will it be?

Dr. Seger:I am sure that personalized medicine, andmore sophisticated drug design may become beneficial in overcoming drug-resistance. My laboratory is currently interested in the Raf/MEK/ERK inhibitors, and a way to overcome their resistance. One of the ways to do itis the use of the anti translocation drugs described above. These drugs affect only the nuclear ERK-targets, and do not target the activity of the cytoplasmic ERK1/2. Therefore, the negative feedback loops that are inhibited by the other inhibitors are not affected, and the problematic hyper-activation of upstream machinery does not occur. As a consequence our approach does not result in the induction of survival pathways, which is one of the main resistant mechanisms of the other inhibitors, and we get a much-prolonged resistance-free period. However, at this stage it seems that we will not be able to completely prevent the resistance to any single drug. Therefore, we might think about combination of sophisticated drugs that will be administered either simultaneously or sequentially to prolong drastically the time to resistance. This may eventually make cancer a "chronic disease" at least until we finally find a way in the far future to beat it completely.

Disease Biology: To you, as a biologist what is your biggest achievement?

Dr. Seger: Although I have some important findings in the field of signal transduction, I consider my successful students as my biggest achievement. More than 70 students and postdocs have been trained so far in my laboratory, and I am proud on the achievement and successes of all of them.

Disease Biology: Sometimes Biology can be synonymous to frustration and failures, particularly if you are in research. What would be your advice to young researchers as well as students for a successful research carrier?

Dr. Seger: Indeed, research can be sometime frustrating. However, I find that hard work and persistence in combination with an open mind will eventually pay off and bring successes even with very tough project.

Disease Biology: What is your opinion and suggestion about initiatives like Disease Biology?

Dr. Seger: I like this initiative, and wish you much of success.