From the Director of the Office of Education

The NHLBI DIR Scientific Retreat is to be held on Monday, May 20th at the Ronald Reagan Building, directly accessible from campus via the Red Line Metro to Metro Center. This is the major event for bringing together all NHLBI DIR scientists, and this promises to be the most well-attended retreat ever. We have over 120 poster submissions, and over 200 registrants. So if you have not yet registered, please do so. Lunch will be provided with generous support of the Foundation for the Advanced Education in the Sciences and NHLBI Principal Investigators. We will present awards for the best poster presentation and also the NHLBI Fellows Award for Research Mentoring and announce the winners of the Lenfant Fellowships. Registration closes on Friday, so please register if you have not already done so.

The summer students are already beginning to arrive on campus, so please take the opportunity to make their stay here a productive one. The Fellows Advisory Committee is already planning a summer social event that will include all NHLBI DIR scientists and staff.

Registration closes Friday, May 10th

11th Annual NHLBI DIR Scientific Retreat
May 20, 2013
The Ronald Reagan Building and International Trade Center
Washington, DC

To register, please visit:
http://dir-intranet.nhlbi.nih.gov/oe/abstractsubmission/default.asp
Recent Publications by NHLBI Fellows


THE SCIENCE BEAT
By Zhiyun Ge, Ph.D.


Interleukin-21 (IL-21) is primarily produced in CD4+ T cells and natural killer T (NKT) cells. As a pleiotropic type I cytokine, IL-21 exerts potent regulatory effects on immune responses by modulating the activation or differentiation of cells like the T cells, B cells, natural killer (NK) cells, NKT cells, and bone-marrow-derived dendritic cells (BMDCs). IL-21 signals via IL-21 receptor (IL-21R) and the common cytokine receptor \( \gamma \) chain, \( \gamma_c \). For instance, when bound to IL-21R, IL-21 activates the JAK/STAT pathway, resulting in the activation of STAT3, which is a major mediator of IL-21 signaling. In contrast to IL-21’s well-studied roles in T cell and B cell activation, its functions in innate immunity is less well understood. It was reported that IL-21 can inhibit the maturation and activation of granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced bone-marrow-derived DCs (GM-CSF-DCs).

In this paper, Wan et al. showed that IL-21 induces apoptosis of conventional DCs (cDCs) in a STAT3- and Bim-dependent manner, and that the apoptotic effect of IL-21 can be reversed by GM-CSF, suggesting that IL-21 and GM-CSF cooperates to modulate the maintenance of immune tolerance and the activation of immune response. First, the authors tested the effects of IL-21 on GM-CSF-DCs and on splenic DCs, which includes conventional DCs (cDCs) and plasmacytoid DCs (pDCs). Results show that IL-21 comprised the cell viability of splenic cDCs by inducing apoptosis, while splenic pDCs and GM-CSF-DCs remained relatively unaffected. Interestingly, the apoptotic effect of IL-21 on cDCs can be reversed by GM-CSF. Additional results show that both IL-21 and GM-CSF has minor effects on MHC class II and CD80 expression in cDCs, indicating that the IL-21-induced apoptosis and maturation maker expression are via two different pathways. Next, the authors performed microarray analysis the study the mechanism of IL-21-induced apoptosis of cDCs and its prevention by GM-CSF. The analysis showed overlapping in the genes the two cytokines regulate. And yet they each have their distinctive regulatory actions on splenic DCs. The microarray analysis also revealed genes that are induced by IL-21 but are suppressed by GM-CSF, among them are \( IL21r \) and \( Bcl211 \) (which encodes Bim).

Considering the role of Bcl-2 family proteins in IL-21-mediated apoptosis in B cells, the authors focused on Bim and showed that IL-21 significantly increases the mRNA and protein levels of Bim, which in turn causes apoptosis of cDCs. Interestingly, GM-CSF can reduce the induction of Bim by IL-21 and thus inhibit the IL-21-induced apoptosis. The authors next showed compelling evidence that STAT3 is also required in IL-21-mediated apoptosis of cDCs. Furthermore, the inhibition effect of GM-CSF on IL-21-induced apoptosis can be attributed to STAT5, whose activation is dependent on GM-CSF. A comprehensive analysis of the genome-wide binding patterns of STAT3 and STAT5 in DCs using the ChIP-Seq experiment suggests a complement between STAT3 and STAT5 for DNA binding, which can possibly explain the ability of GM-CSF to inhibit IL-21’s effect on DCs. Consistent with the effects of IL-21 and GM-CSF on DCs in vitro, the in vivo data indicates that IL-21-induced cDC death requires the expression of IL-21 receptor, STAT3 and Bim. Moreover, the GM-CSF induced STAT5 is also a negative regulator of IL-21’s effects in vivo.

The authors then sought to study the physiological role of IL-21 on DCs. It is known that the activation of NKT cells by glycolipid \( \alpha \)-galactosylceramide (\( \alpha \)-GalCer) induces the expression of IL-21. NKT cells in WT mice repetitively challenged with \( \alpha \)-GalCer injections produced high level of IL-21 rapidly but showed decreased GM-CSF production. In addition, repetitive injections of \( \alpha \)-GalCer decreased the number of CD8+ but not CD8+ splenic DCs and the decrease of CD8+ can be attenuated without IL-21R and Bim, suggesting that IL-21 regulates DC numbers via the induction of Bim in vivo. The authors then showed evidence that IL-21 inhibits GM-CSF production in CD4+ cells, indicating cross-regulatory effects of the two cytokines. Finally, the functional role of IL-21 on DCs in a disease setting was explored, using a T cell adoptive transfer colitis model, confirming the role of IL-21 on DC turnover and T-cell mediated pathology.
What determines a successful postdoctoral experience? The simple answer is that it is one that gets you the credentials to successfully compete for the job that you want. Because different jobs have different requirements, it becomes important early on to identify the requirements for the job you want and map out how to acquire them. When they appear on your c.v. or resume, they become the way potential employers can evaluate you against the job requirements. The implication is that employers will evaluate you as a whole, rather than in parts, though there are skills that are essential for certain positions. Thus, if you are seeking an academic position as a principal investigator, your publication record becomes important, as does your ability to define and execute a novel research project. On the other hand, if you are interested in public policy, interpersonal interactions and the ability to work as part of a team may be more important.

So how do academic employers evaluate your publication record? According to Dr. Richard Nowakowski, chair of the Department of Biomedical Sciences at Florida State University, you might envision your record as a “score” computed as a function of the quality of your publications and their frequency of appearance. Thus, each time you publish, you increase your “score”, with larger increases for higher quality papers. This score then decays with a half-life. So each time you publish you raise your score, but if you publish infrequently, your score will decay faster than it is increased. If you wait too long, then your score could drop to zero. So if you haven’t published in a while, you need to be very realistic about the need to publish every year or two to keep your score above zero.

Your ability to define and execute a research project is something that can also be documented. Thus, if your publications, both as a graduate student and postdoc, are novel and take your advisor’s lab into new directions, you will receive credit. Further evidence would be if you are successful in competing for a fellowship or grant, each of which requires a research proposal.

If your job goal is public policy, you can document your ability to work as a team by participating in activities on the NIH campus, such as the NHLBI Fellows Advisory Committee or FELCOM. In addition, you can do a rotation in Science Policy as part of your fellowship.

The bottom line is that adequate planning can ensure that you have the credentials you need to be competitive.