Eight Members Honored with the VICB “High Impact Publication Award” - The VICB is pleased to announce the recipients of the 2014 High Impact Publication Award. In this second year of the annual prize, we honor the communicating authors of six highly cited publications. Data used to select the recipients were collected in early January of 2014 for papers published in 2011. The awardees are:

Jennifer Pietenpol, for “Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies” [B.D. Lehman, J.A. Bauer, et al. (2011) J. Clin. Invest., 121, 2750]. A particularly aggressive disease, triple negative breast cancer (TNBC) lacks the estrogen, progesterone, and Her2 receptors against which many of the most effective therapies are targeted. The diversity of the disease further complicates treatment. The Pietenpol lab used gene expression data from 21 publicly available data sets encompassing 3,247 primary breast cancers to identify 587 TNBC tumors. Statistical analysis using k-means clustering and consensus clustering identified seven subtypes of TNBC based on distinctive patterns of gene expression. Twenty-seven of thirty cultured TNBC cell lines investigated by the researchers could be classified into one of the subtypes, providing preclinical models for further study. Of particular importance was the finding that the subtypes exhibited differential sensitivity to various chemotherapeutic agents, providing the foundation for a more rational approach to the treatment of TNBC. In fact, this work has led to a clinical trial of anti-androgen therapy for the treatment of one of the subtypes identified in the study.

Eric Skaar and Walter Chazin, for “Nutrient metal sequestration by calprotectin inhibits bacterial superoxide defense, enhancing neutrophil killing of Staphylococcus aureus” [T.E. Kehl-Fie, et al. (2011) Cell Host Microbe, 10, 158]. During the course of infection, bacteria must acquire critical nutrients from the host. Sequestration of nutrients by the host, a process known as “nutritional immunity,” can contribute significantly to the control of infection. One mechanism of nutritional immunity is the sequestration of Zn²⁺ and Mn²⁺ by the neutrophil protein calprotectin (CP). To better understand exactly how CP inhibits the growth of S. aureus, the Skaar and Chazin labs focused on the enzyme superoxide dismutase (SOD), both forms of which require Mn²⁺ in S. aureus. The investigators showed that CP exposure reduced SOD activity and increased superoxide levels in S. aureus. Consistently CP increased the sensitivity of the bacteria to superoxide stress, an effect that was reversed by excess Mn²⁺. In contrast, a mutant CP protein that could not bind Mn²⁺ was not able to increase superoxide sensitivity of cultured S. aureus. Mice genetically engineered to lack CP were more susceptible to infection by wild-type S. aureus, but not S. aureus expressing inactive mutant forms of SOD. Together the data support the conclusion that sequestration of Mn²⁺ by CP prevents the synthesis of active SOD in S. aureus, resulting in increased sensitivity of the bacteria to oxidative stress.

David Cortez, for “Analysis of protein dynamics at active, stalled, and collapsed replication forks” [B.M. Sirbu, et al. (2011) Genes Dev., 25, 1320]. The DNA damage response (DDR) to replication stress has been difficult to study due to the technical challenges surrounding site-specific analysis of active versus stalled replisomes. The Cortez lab has met this challenge with iPOND (isolation of proteins versus stalled replisomes). The Cortez lab has met this challenge with iPOND (isolation of proteins versus stalled replisomes). The iPOND approach to cells undergoing hydroxyurea-mediated replication stress allowed the researchers to monitor the evolution of the early response to the stress and the eventual accumulation of DDR proteins once double-strand breaks had formed at collapsed replication forks. Clearly iPOND provides...
a powerful new approach to interrogate the dynamics of both normal and stalled DNA replication.

Larry Zwiebel, for “Functional agonism of insect odorant receptor ion channels” [P.L. Jones, et al. (2011) Proc. Natl. Acad. Sci. U.S.A., 108, 8821]. Mosquitoes seek out their blood meal hosts through their sense of smell. Odors are detected through odorant-gated ion channels comprising an odorant receptor (OR) protein and an OR coreceptor protein (Orco) in a complex of unknown stoichiometry. In collaboration with the VICB HTS Core, the Zwiebel lab devised a calcium imaging screen of odorant channel function. Screening the >100,000 compounds in the VICB library revealed compound VUAA1, an allosteric agonist of channel function. The researchers demonstrated that VUAA1 facilitates odorant channel function in the presence or absence of an odorant. Furthermore, they discovered that the Orco protein forms an ion channel in the absence of an OR protein, and VUAA1 acts directly on Orco from mosquitoes as well as a number of disparate insect species. Clearly, VUAA1 is a valuable probe of odorant channel function and of the Orco protein, specifically. Its discovery also paves the way for the exploration of small molecules that can disrupt insect behaviors on the basis of modulating olfaction.

Seva Gurevich, for “Monomeric rhodopsin is sufficient for normal rhodopsin kinase (GRK1) phosphorylation and arrestin-1 binding” [T.H. Bayburt, et al. (2011) J. Biol. Chem. 286, 1420]. After rhodopsin (Rh) is activated by light, it is phosphorylated by GRK1. Then, binding of arrestin-1 to the phosphorylated receptor (P-Rh*) prevents further activation of the G protein transducin, putting an end to the signaling cascade. Rh forms dimers and higher oligomers in photoreceptor membranes, leading to a controversy regarding the actual functional state of the receptor. To address this question with regard to the interaction between P-Rh* and arrestin-1, the Gurevich lab, in collaboration with Stephen Sligar (U. of Illinois) and his laboratory, created lipoprotein nanodiscs containing an isolated Rh molecule. The researchers showed that GRK1 phosphorylated activated Rh in the nanodiscs more efficiently than in native membranes. Furthermore, arrestin-1 bound P-Rh* in nanodiscs with high affinity and 1:1 stoichiometry. These results clearly indicate that monomeric Rh is fully functional with respect to both GRK1 phosphorylation and interaction with arrestin-1.

Jennifer Pietenpol, for “Interaction of a G protein with an activated receptor opens the interdomain interface in the alpha subunit” [N. Van Eps, et al. (2011) Proc. Natl. Acad. Sci. U.S.A., 108, 9420]. The alpha subunit of heterotrimeric G proteins (Gα) contains GDP in the inactive state, which it exchanges for GTP upon binding to a ligand-activated G protein-coupled receptor. Gα comprises two domains, a nucleotide binding domain and a helical domain. The helical domain partially occludes the GDP bound in the nucleotide binding domain. Thus, a movement of the two domains relative to one another is required for nucleotide exchange. To explore this process in greater detail, the Meiler and Hamm laboratories, in collaboration with Wayne Hubbell’s laboratory (UCLA), constructed multiple Gα proteins, each bearing one site-directed spin label in the nucleotide binding domain and one in the helical domain. They used these proteins to conduct double electron-electron resonance (DEER) spectroscopy to monitor the movement of the Gα domains during binding of the heterotrimeric G protein to activated rhodopsin and the subsequent nucleotide exchange. These data provided the foundation for construction of a model of Gα conformational changes throughout these processes. The model predicts that binding of a ligand-activated receptor to the C-terminal helix of Gα induces a movement of the helical domain away from the nucleotide binding domain. The motion entails a 8 Å translation and 29° rotation. The result is increased flexibility in the subunit and an opening of the nucleotide binding site that allows GDP to GTP exchange to occur.

Seva Gurevich

— IMPORTANT DATES —

VICB Seminar Schedule

There are still some great seminars remaining in the spring series. Be there!

The following seminars are at 12:15 PM in 1220 MRB III:

Mar 5......David Spiegel, Yale University
Mar 19....Maria Hadjifrangiskou, Vanderbilt University
Apr 9......Andrea Robitzi, Leipzig University
Apr 23.....Heather Maynard, University of California - LA
Apr 30.....Kate Carroll, Scripps Research Institute
May 7 .....Jennifer Pietenpol, Vanderbilt University

For reminders of upcoming VICB seminars and events as well as the latest news from the world of chemical biology, follow us on Twitter: @VICB_Vanderbilt!