SCHOOL OF MEDICINE & DENTISTRY
UNIVERSITY of ROCHESTER MEDICAL CENTER

2023 PREP Symposium

June 13, 2023

Program Directors

Jacques Robert, PhD & Elaine M. Smolock, PhD

Presentations

Time	Name	Title; *Advisor*
1:00pm-1:15pm		**Introduction**
1:15pm-1:30pm	**Jose Reynoso**	**Effects of expertise and age on reaching movements guided by vision, memory, and proprioception** *Advisor: Duje Tadin, PhD*
1:30pm-1:45pm	**Jacob Cody Naccarato**	**A structure-function analysis of the PR-domain in MECOM in the context of MLL-AF9 leukemia** *Advisor: Archibald Perkins, PhD*
1:45pm-2:00pm	**Hunter Houseman-Eddings**	**Investigating the effects of interferon-stimulated gene TMEM140 on poxvirus infection** *Advisors: Brian Ward, PhD*
2:00pm-2:15pm	**Jackie Agyemang**	**Effect of maternal Bisphenol A (BPA) exposure on pregnancy loss in mice** *Advisor: Martha Susiarjo, PhD*
2:15pm-2:30pm	**Lourdes Marinna Caro Rivera**	**The role of immune metabolism in bone marrow megakaryocyte immune differentiation** *Advisor: Craig Morrell, PhD*
2:30pm-2:45pm	**Aaron Huynh**	**Assessing relationships between neuroinflammation markers and cognitive function in patients with breast cancer** *Advisors: Michelle Janelsins, PhD; AnnaLynn Williams, PhD*
2:45pm-3:00pm		**Questions**
3:00pm – 4:00pm		**Reception in the Microbiology and Immunology Break Room** *2nd floor MRBX*

Effects of expertise and age on reaching movements guided by vision, memory, and proprioception

Jose Reynoso and Duje Tadin

Our ability to effortlessly sense our self-movement in space is a proprioceptive ability that is often overlooked. Without proprioception, a mundane task such as typing can become a time-consuming task. We recently showed how virtual reality (VR) can be used to quickly and precisely measure reaching behavior and offers easy ways to isolate the effects of proprioception and memory (Isenstein et. al., 2022, Plos ONE). In our published work, we found a large amount of individual variability in the reaching accuracy. This motivated our hypothesis that this variability may be due to individual differences in experiences with self-movement, such as dancing. In dance, precise and rhythmic movements are integral to the performance and are often done without the full use of vision. Yet, proprioception seems to be underassessed within the field of dance. In the current study, we aimed to elucidate the effects of expertise and age on reaching behavior. The subject's task was to simply reach out forward to "touch" a virtual ball. Critically, the subject's hand was either visible (rendered in VR) or invisible; a manipulation used to isolate proprioception. To assess effects of memory, subjects reach for the target 1 second after it was made invisible. Interestingly, after testing 18 dancers and 19 non-dancers, we found no significant differences in the accuracy of reaching movements guided, in separate conditions, by vision, proprioception, or memory. Next, we investigated effects of age on vision- and proprioception-guided movements in 18 older adults (ages 58-74 years). We found a significant correlation between age and the accuracy of proprioception-guided movements ($r=0.44$, $p=0.032$, one tailed), but not between age and visually guided movements. This suggests that effects of age become more prominent when subjects cannot rely on vision to aid their movements. In summary, we found that dance experience does not affect the accuracy of reaching behavior. In contrast, we found that aging does affect reaching behavior, especially when vision of the movement is unavailable.

A structure-function analysis of the PR-Domain in MECOM in the context of MLL-AF9 leukemia

Jacob Cody Naccarato and Archibald Perkins

Acute myeloid leukemia (AML) is a blood cancer which disrupts normal blood production concomitant with expansion of leukemic cells. AML represents a diverse group of disorders resulting from various somatically acquired point mutations and/or chromosomal rearrangements. One such rearrangement, t(9; 11)(p22;q23), results in a form of leukemia caused by a fusion protein, MLL-AF9, which has especially poor prognosis and limited treatment options. With the long-term goal is to develop novel treatment options for this aggressive AML subtype, we are expanding on previous work regarding the Positive Regulatory Domain (PR-domain) of the PRDM3 isoform of *MECOM*. Previously, we have shown that survival of MLL-AF9 AML cells is dependent on a functional PR-domain. When the PR-domain is knocked-out of mouse hematopoietic stem cells, leukemogenesis is not possible. To better understand which parts of the PR-domain are important, we are performing a structure-function analysis to identify possible targets for small molecule drugs. This involves the systematic mutation of various sites of interest along the PR-domain in the context of MLL-AF9 driven leukemia. This process is performed in mouse bone marrow cells with a MECOM knockout phenotype. Amino-acid changes that result in a halt to the leukemogenesis process represent potential sites of drug targeting. At present, we have 26 mutation sites being studied with ongoing preliminary data being collected.

Investigating the effects of interferon-stimulated gene TMEM140 on poxvirus infection

Hunter Houseman-Eddings and Brian Ward

The host's innate immune system is the first line of defense against viral infection. An important component of this is the interferon response, which induces expression of a wide array of interferon-stimulated genes (ISGs). These genes can have broad or specific antiviral activity through diverse mechanisms. In order to establish a successful infection, viruses have evolved mechanisms of avoiding and antagonizing ISGs. Poxviruses encode many such strategies, including several genes that inhibit the interferon pathway itself. Studying interactions between poxviruses and the host innate immune response can reveal information about both the virus and the host's response. To probe these interactions, an siRNA screen was performed in vaccinia virus infected cells, and change in viral gene expression was measured. Knockdown of transmembrane protein 140 (TMEM140) strongly increased viral early gene expression. TMEM140 is a multi-pass transmembrane protein that has previously been identified to affect early stages of the retroviral life cycle. Studies are being undertaken to validate the hit and to further understand the impact of TMEM140 on vaccinia virus infection.

Effect of maternal Bisphenol A (BPA) exposure on pregnancy loss in mice

J. Agyemang, J. Reed, P. Spinelli, and M. Susiarjo

Bisphenol A (BPA) is a ubiquitous environmental contaminant found in various consumer products. Exposure to BPA is associated with pregnancy loss in human and animal studies. One mechanism of pregnancy loss is aberrant maternal-fetal immune tolerance. Regulatory T cells (Treg) are critical moderators of maternal immune tolerance and their expansion during pregnancy downregulates pro-inflammatory signaling molecules. Our lab recently reported that exposure to BPA results in higher rates of hemorrhaging and resorption of allogeneic mouse conceptuses generated from mating of CBA female to C57BL/6 male mice (CBA x BL6). These changes were correlated with decreased Tregs number in maternal tissues from BPA exposed-CBA female mice relative to controls. The aim of this study is to test whether similar findings are observed in allogeneic conceptuses generated from C57BL/6 females mated to CBA males (BL6 x CBA), and syngeneic conceptuses from CBA females mated to CBA males (CBA x CBA). The previous allogeneic mating (CBA x C57BL/6 males) was repeated and used as a positive control for expected bpa-induced pregnancy loss. Conceptuses were microscopically harvested, analyzed at embryonic day (E) E7.5 by two blinded individuals. Hematoxylin and eosin (H&E) staining of decidual capsules was performed to study the histopathology of the hemorrhaging phenotype. BPA induced pregnancy loss was not observed in conceptuses from allogeneic (BL6 x CBA) pregnancies (0% hemorrhaging; dams (N=13); conceptuses (n =96)). The rate of hemorrhaging in syngeneic pregnancies (CBA x CBA) was unexpectedly high in controls (32.58%; N=15;n=89) compared to BPA (18.60%; N=15; n=86). Hematoxylin and eosin (H&E) staining of decidual capsules show mononuclear cell infiltration in hemorrhaging conceptuses, thus serving as a possible efficient method of identifying hemorrhaging events.

The role of immune metabolism in bone marrow megakaryocyte immune differentiation

Lourdes Marinna Caro-Rivera, Alison C. Livada, and Craig N. Morrell

Megakaryocytes (Mks) differentiate from hematopoietic stem cells which generate all of the blood's cellular components. Mks are large hematopoietic cells in the bone marrow specialized to produce and release platelets into circulation. Platelets act as the first line of defense at the interface of thrombosis and immunity – platelets form thrombi at sites of vascular lesions, but also secrete molecules that induce different immune responses, such as the recruitment of neutrophils and monocytes and biasing T and B cell development. Previous research indicates that Mks can also behave as immune and inflammatory cells. There is evidence that lung Mks display higher immune properties in comparison with bone marrow Mks. Immune stimuli such as interleukin (IL)-33 are known to drive immune cell differentiation and induce trained immunity leading to a change in metabolism profiles. Using an *ex vivo* approach stimulating primary Mks isolated from the bone marrow with IL-33, we showed an upregulation of MHCII and ICAM-1 expression compared to control Mks. The literature indicates that Mks may use multiple metabolic pathways. Glucose metabolism is required for Mk platelet production. We have found that incubating Mks with a non-hydrolyzed glucose, 2-deoxy-D-glucose (2DG), limits IL-33 induced MHCII and ICAM-1 expressions. These studies will help us identify if immune stimuli change Mk metabolic pathways and if tissue environments influence Mk metabolism.

Assessing relationships between neuroinflammation markers and cognitive function in patients with breast cancer

Aaron N.L. Huynh, AnnaLynn M. Williams, Paige Van Haute, Louis T. Lotta, Bryan Thompson, Colleen Netherby-Winslow, Elizabeth K. Belcher, Sara Alberti, Emma Bentley, Eva Culakova, Michelle C. Janelsins

Aside from the physically debilitating symptoms of the disease and side effects of treatment, a significant proportion of patients with cancer diagnoses may experience cancer-related cognitive decline (CRCD); more commonly known as “chemo-brain”. CRCD should be taken as an important clinical consideration: it can cause patients to experience problems with formerly “simple” tasks in their day-to-day lives, subsequently lowering their quality of life. Specifically, CRCD elicits deficits in cognitive domains of memory, attention, and executive functioning, however the mechanism for this clinical phenomenon is not extensively studied. Previous literature has shown that elevated S100β, a calcium-binding protein commonly found in glial cells, can exhibit neurotoxic effects, including disruption of the blood-brain barrier (BBB), during neuroinflammation following chemotherapy. Given the potential deleterious effects, S100β may serve as a biomarker of acute CRCD in our nationwide cohort of breast cancer patients. Via 22 National Cancer Institute Community Oncology Research Program (NCORP) locations, we consented 943 participants – 580 of which were patients with breast cancer and 363 of which were age-matched, noncancer controls. We subset this population for participants with serum samples available at both available collection timepoints (pre- and post-chemotherapy), leaving us with 505 patients with breast cancer and 336 age-matched, noncancer controls. Through Welch’s two-sample t-tests, multivariate linear regressions, and Spearman rank correlations, we investigated the longitudinal changes in serum S100β concentrations and their relationships to changes in neurocognitive outcomes over time. We observed an increase in S100β for patients with breast cancer (Paired t-test of log transformed serum S100β; $p = 0.004$), but not for noncancer controls over time ($p = 0.634$). Additionally, we identified subtle relationships between changes in serum S100β and worsening changes in cognitive performance (Spearman Rank Correlation Coefficients range: [-0.10, 0.11]; p-value range: [0.025, 0.979]).

Thank you to everyone involved in URMC-PREP!

Mentors, Bench Mentors, & Committee Members

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