exposures to both sunitinib and to increases in afterload will augment sunitinib toxicity in CMTs via the primary outcomes mentioned in Aim 1. Additionally, we hypothesize that decreases in afterload will decrease effective sunitinib toxicity in CMTs via the primary outcomes mentioned in Aim 1. Aim 3: We hypothesize that exposure to an AMP-kinase activator but not carvedilol will decrease the effects of sunitinib toxicity in CMTs via the primary outcomes mentioned in Aim 1. DISCUSSION/SIGNIFICANCE OF IMPACT: The use of small molecule, targeted chemotherapeutic agents is increasingly common. Many of these agents cause cardiotoxic side effects, the mechanisms of which are incompletely understood. Our lab has developed a novel 3D tissue engineering platform capable of supporting durable in vitro cardiac microtissues that experience dynamic alterations in their biomechanical load. By using this platform to examine the cardiotoxic effects of sunitinib, insight into treatment and prevention of this common problem will be developed.

3127

The effect of common genetic variants in the oxytocin receptor gene on oxytocin response.

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OBJECTIVES/SPECIFIC AIMS: Previous studies suggest that genetic variants in the oxytocin receptor (OXTR) may alter oxytocin dose requirement for labor induction and may increase risk for preterm labor and neurodevelopmental disorders. However, the mechanisms of actions of these variants remain unknown. The goal of this study was to functionally characterize common missense and noncoding variants in OXTR. First, we aimed to determine the effects of missense variants on two major aspects of receptor function: calcium signaling and β-arrestin recruitment. Second, we used allelic expression imbalance assays in an effort to identify regulatory single nucleotide polymorphisms (SNPs) in noncoding regions of OXTR that alter OXTR mRNA expression. METHODS/STUDY POPULATION: We used the Exome Aggregation Consortium database to identify the 12 most prevalent missense single nucleotide variants in OXTR. To determine the functional effects of these variants, we transfected human embryonic kidney cells (a common model system used to study receptor function) with wild type OXTR, variant OXTR, or empty vector control. We used the calcium-sensitive dye Fluo4 to quantify intracellular calcium flux in response to oxytocin treatment, and used bioluminescence resonance energy transfer assays to measure recruitment of the signaling partner β-arrestin to the receptor. To investigate potential effects of noncoding SNPs on OXTR mRNA expression, we quantified allele-specific expression of OXTR in human uterine tissue obtained from participants at the time of Cesarean section. We used next-generation sequencing (Illumina MiSeq) to count alleles of a reporter SNP in OXTR exon 3. RESULTS/ANTICIPATED RESULTS: Of the 12 most prevalent missense single nucleotide variants, four were predicted to be deleterious by PolyPhen variant annotation software. We anticipate that these variants will alter receptor signaling through calcium or β-arrestin pathways. We further observed that a reporter SNP in OXTR exon 3 exhibits significant allelic expression imbalance in a subset of our myometrial tissue samples, indicating that OXTR expression may be regulated by a functional SNP. Our current work focuses on discovering the functional SNPs in OXTR responsible for the pattern of allelic expression imbalance seen in mRNA. In the future, we will seek to explore the effects of these variants on uterine function by using genome editing of uterine smooth muscle cells. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results suggest that both missense and noncoding variants may affect OXTR expression and function. Future studies may suggest that OXTR sequencing, genotyping, or expression analysis would be useful to identify individuals likely to respond or fail to respond to safe doses of oxytocin for labor induction. Personalizing approaches for labor induction in this way would increase the safety of oxytocin and potentially reduce maternal morbidity and mortality.

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The Effects of Aging on the Rectal Mucosal CD4+ T cell Compartment and its Implications for HIV Transmission

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OBJECTIVES/SPECIFIC AIMS: In the first aim, we will evaluate the proportion of highly HIV-susceptible memory CD4+ T cells present in the rectal mucosa, based on the proliferation status and expression of the HIV susceptibility markers, CCR5 and α4β7, between HIV-negative adolescent MSM and adult MSM engaging in RAI. The second aim will assess differences between the two study groups in the ratio of Th17 cells (CD4+ IL17+) to Treg cells (CD4+ FoxP3+ CD25+) in the rectal mucosa as a determinant of mucosal inflammation. Finally, in the third aim, we will utilize ex vivo rectal biopsy explant challenge experiments to examine whether HIV target cell availability and the Th17/Treg ratio influence rectal mucosal HIV susceptibility. METHODS/STUDY POPULATION: Rectal biopsy specimens are being collected from healthy, HIV-negative men that comprise the two study groups: 40 adolescent MSM 18-21 years of age who have engaged in RAI at least once previously in their lifetime and 40 adult MSM ≥35 years of age who have engaged in RAI for the previous 5 consecutive years with a minimum of 12 episodes annually. To identify CD4+ subsets of interest for aims 1 and 2, rectal mucosal mononuclear cells are isolated and phenotyped with CD45, CD3, CD4, CD45RA, CCR7, CD69, CCR5, α4β7, Ki67, FOXP3, and CD25 antibodies. To identify the Th17 cell subtype, the cells are stimulated with PMA/Ionamycin and stained with an antibody specific to IL-17A. Using cross-sectional analyses, we will compare the frequencies of mucosal CD4+ T cells that express certain phenotypic characteristics and evaluate differences in the Th17/Treg ratio between adolescent and adult MSM. For aim 3, rectal biopsy specimens are inoculated with HIV virus and the culture supernatant is assayed for p24 concentration on days 3, 7, 10 14, and 18. Longitudinal analyses will be performed to detect differences in p24 concentration at each time point and assess associations with mucosal target cell availability and with the Th17/Treg ratio. RESULTS/ANTICIPATED RESULTS: We hypothesize that younger age will be associated with enhanced memory CD4+ T cell proliferation and increased expression of HIV susceptibility markers (CCR5 and/or α4β7). In addition, we expect that the rectal mucosa of adolescent MSM will demonstrate a higher Th17/Treg ratio as compared to adult MSM, which could facilitate HIV transmission. It is also anticipated that rectal mucosal immune phenotypes characterized by increased HIV target cell availability and high Th17/Treg ratios

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will be associated with enhanced mucosal HIV susceptibility in the explant challenge model. DISCUSSION/SIGNIFICANCE OF IMPACT: There is a paucity of information regarding the mechanisms of rectal HIV transmission, and no studies to date investigate the immunologic effects of aging on transmission in the rectal mucosa. The results from this study will provide important information regarding age-related differences in the immune cell composition of the rectal mucosa as a critical step in better understanding immunologic factors that influence rectal HIV transmission.

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Toxicity of Released B Cell Products in Multiple Sclerosis: Effects on Neurons and Oligodendrocytes

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OBJECTIVES/SPECIFIC AIMS: We previously demonstrated that products released by cultured B cells from patients with Multiple Sclerosis (MS) are cytotoxic to neurons and oligodendrocytes, while minimal toxicity was observed in response to B cell secretory products from age- and sex-matched normal controls. The goal of this proposal is to identify the range of brain cells susceptible to MS B cell-mediated cytotoxicity, to define the cytotoxic factor(s) released by MS B cells, and to determine whether particular subset(s) of MS B cells harbor the greatest pathogenic potential. METHODS/STUDY POPULATION: The toxicity of B cell products will be demonstrated by incubating primary rat cultures of neurons, oligodendrocytes, and oligodendrocyte progenitor cells (OPCs) with B cell supernatants. B cells will be isolated from the peripheral circulation of untreated relapse-remitting MS (RRMS) patients and age- and sex-matched normal controls. The identification of specific toxic factor(s) in MS B cell supernatants will be achieved through a combination of exosome-depletion/enrichment of conditioned media, proteomics, next generation sequencing, and lipidomics. Determining pathogenic B cell subsets will be achieved by cell sorting into memory and naïve B cell subsets prior to collection of supernatants. RESULTS/ANTICIPATED RESULTS: We hypothesize that the toxicity of MS B cell products is mediated, at least in part, by extracellular vesicles, such as exosomes. We expect depletion of these exosomes from the B cell conditioned media or inhibition of their biogenesis will mitigate the observed toxicity. Furthermore, differences in B cell-derived exosomal content, such as proteins, (mi)RNAs, or lipids, likely explain the differences in observed toxicity. Lastly, we hypothesize that memory B cells, which are enriched in the CNS of MS patients and demonstrate a more pro-inflammatory profile than naïve B cells, are responsible for the toxicity observed in supernatants of total B cells. DISCUSSION/SIGNIFICANCE OF IMPACT: MS is the most prevalent chronic inflammatory disease of the CNS, affecting more than 2 million people worldwide. Although over a dozen disease-modifying therapies are approved for the treatment of RRMS, none are meaningfully effective at limiting disease progression. This proposal will provide new insight into immune-CNS interactions in progressive MS and provide much-needed novel targets for therapeutic intervention, either via blocking identified toxic molecule(s) or by selectively depleting pathogenic B cell subsets.

Regulatory Science & Translational Methods

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Columbia University's Personalized IRB Liaison Service: Evaluation over its initial 2.5 years

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OBJECTIVES/SPECIFIC AIMS: National concerns about IRB-related research delays have led to re-assessment of IRB review processes at institutional levels. We sought to address whether a dedicated IRB Liaison Service at the Irving Institute's central location could provide additional useful staff support to the investigator community for interactions with the IRB at various levels of protocol submission. METHODS/STUDY POPULATION: We evaluated the results of a user satisfaction survey and performed a focused in-depth analysis of Liaison Service impact. An online tracking and satisfaction survey was implemented for researchers to complete following each consultation. The goal was to gauge the uses, user types and usefulness of the Service, and to follow-up with researchers who might have additional questions. Data was gathered about users of the Service and their affiliations, and the topics and questions that were discussed. A terse summary was drafted to categorize each consultation that was conducted during office hour sessions. Additionally, surveys were emailed to researchers to gauge their experience with the Service and their overall satisfaction. Users completed the survey either in person at the end of the consultation, or by email request sent immediately following each in-person consultation. The impact of the IRB Liaison Service on IRB protocol approval times was analyzed for a random sub-sample of protocols for which consultations were provided. Consultations for studies with an associated IRB protocol number (i.e., at least initially submitted) from May 2015-June 2017 had been assigned a number in an Excel file. Using a randomization formula, a subset of 90 protocols was identified for further analysis. Protocols that did not result in an IRB submission and duplicate entries were removed. The final dataset consisted of 67 protocols. Those protocols were assessed by type of review process (expedited versus full board review), by status (new submission, first return, second return, etc.), and by which of the seven IRB committees completed the review. Consultations for each protocol included in this subset were reviewed using the notes about that consultation. IRB records in Columbia's online research oversight system, Rascal, were also reviewed to assess the timing of and issues raised in subsequent IRB review. Factors examined included whether the protocol was approved at next submission and if not, whether questions raised in subsequent IRB returns were related to the topics discussed in the consultation. RESULTS/ANTICIPATED RESULTS: Since its inception in January 2015 through June 2017 (2.5 years), a total of 501 in-person consultations have been performed, usually 25-30 per month. Users were primarily study coordinators and investigators. Most requests concerned new protocol development, policy questions or assistance in addressing IRB comments from submitted protocols. Survey response rate was 43%. Results of 215 competed satisfaction surveys were 100% positive. Of 67 unique protocols analyzed for outcomes of the consultation, 73% were subsequently approved within 14 days. DISCUSSION/SIGNIFICANCE OF IMPACT: Overall, we

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