1) Saurabh Gawde, Postdoc, Immunology and Rheumatology

Title: Tobacco Smoking Increases Inflammatory Disease Activity and Serum Levels of S100 Proteins and Class-Switched Memory B cells in MS Patients

Abstract: Multiple sclerosis (MS) is an autoimmune disease that attacks the central nervous system (CNS), leading to destruction of neurons and rendering patients disabled. Health factors like diet, body mass index (BMI), sunlight exposure, vitamin D levels, and tobacco smoking can affect the prognosis of MS patients. Tobacco smoking, in particular, has been associated with increased disease activity in relapsing remitting (RR) MS. However, the biological mechanisms behind smoking increasing disease activity have not been identified.

2) Preksha Bhagchandani, Graduate Student, Immunology

Title: Hematopoietic stem cell transplantation promotes islet transplant tolerance and autoimmune diabetes reversal

Abstract: Although islet transplantation holds promise as a curative approach in type 1 diabetes, physicians and scientists are challenged to produce safe immunosuppression-free methods to promote islet transplant tolerance. Mixed chimerism achieved by hematopoietic cell transplantation (HCT) promotes tolerance of transplanted donor-matched solid organs and corrects autoimmunity, but requires the development and improvement of non-toxic bone marrow conditioning protocols to expand clinical use. We developed a chemotherapy-free, non-myeloablative conditioning regimen that achieves mixed chimerism and allograft tolerance across major histocompatibility complex (MHC) barriers. Durable multi-lineage mixed chimerism was achieved in immunocompetent pre-diabetic NOD mice using monoclonal antibody targeting of c-Kit, T-cell depleting antibodies, JAK-STAT inhibition, and low dose total body irradiation prior to transplantation of hematopoietic cells, which prevented diabetes in 100% of mice (n = 14). We then applied this reduced-intensity conditioning protocol to diabetic NOD mice after autoimmune destruction of islets. After confirmation of diabetes and
conditioning, MHC-mismatched donor-matched islets and bone marrow were transplanted, resulting in 100% long-term correction of diabetes (n = 9) without chronic immunosuppression or graft-versus-host disease (GVHD). Treated mice remained immunocompetent, assessed by complete blood counts and ability to reject foreign 3rd party allogeneic islets. Adoptive transfer of T cells from mixed chimeras into diabetes susceptible NOD RagKO does not transfer diabetes. Studies of chimerism in NOD reveal deletion of autoreactive host T cells and host-reactive donor T cells, important mechanisms of tolerance. These results provide proof-of-concept for a clinically-translatable reduced-intensity conditioning regimen and cell transplantation protocol that achieve durable hematopoietic chimerism, promoting islet allograft tolerance and type 1 diabetes reversal.

3) Ivana Cvijovic, Postdoc, Applied Physics

Title: Long-term B cell memory emerges at uniform relative rates in the human immune response

Abstract: B cells generate pathogen-specific antibodies and play an essential role in providing adaptive protection against infection. Antibody genes are modified in evolutionary processes acting on the B cell populations within an individual. These populations proliferate, differentiate, and migrate to long-term niches in the body. However, the dynamics of these processes in the human immune system are primarily inferred from mouse studies. We addressed this gap by sequencing the antibody repertoire and transcriptomes from single B cells in four immune-rich tissues from six individuals. We find that B cells descended from the same pre-B cell (“lineages”) often co-localize within the same tissue, with the bone marrow harboring the largest excess of lineages without representation in other tissues. Within lineages, cells with different levels of somatic hypermutation are uniformly distributed among tissues and functional states. This suggests that the relative probabilities of localization and differentiation outcomes change negligibly during affinity maturation, and quantitatively agrees with a simple dynamical model of B cell differentiation. While lineages strongly co-localize, we find individual B cells nevertheless make independent differentiation decisions. Proliferative antibody secreting cells, however, deviate from these global patterns. These cells are often clonally expanded, their clones appear universally distributed among all sampled organs, and form lineages with an excess of cells of the same type. Collectively, our findings show the limits of peripheral blood monitoring of the immune repertoire, and provide a probabilistic model of the dynamics of antibody memory formation in humans.
4) Laura van Dam, Postdoc, Immunology & Rheumatology

Title: Identification of autoreactive cytotoxic T cells in ANCA-associated vasculitis

Abstract: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare and severe autoimmune disease, characterized by a pauci-immune necrotizing vasculitis leading to inflammation and damage of major organs. In AAV, autoantibodies against neutrophil cytoplasmic antigens, including proteinase-3 (PR3) or myeloperoxidase (MPO), and the ANCA producing B cells play a central role in the pathogenesis. Autoreactive T cells and their features are less well-studied, but recent studies suggest their importance in the pathogenesis of AAV.

5) Yuhsin Vivian Huang, Staff, Stanford Cardiovascular Institute

Title: Targeting the CXCR3-CXCL9/10 Axis to Treat Immune Checkpoint Inhibitor-mediated Myocarditis

Abstract: Immune checkpoint inhibitors (ICIs) are successful in treating many cancers but may cause immune-related adverse events. ICI-mediated myocarditis has a high fatality rate of up to 40%, with severe cardiovascular consequences. Targeted therapies for ICI myocarditis are currently lacking.

6) Clarence Rachel Villanueva, Staff, Immunology

Title: Anti-B cell therapy may prevent the production of autoreactive B cells in relapsing remitting multiple sclerosis

Abstract: B-cell depleting monoclonal antibodies have proven to be extremely potent in reducing or stopping disease activity in relapsing remitting multiple sclerosis (rrMS). The long-term effect of anti-B cell therapy in rrMS contrasts with its short-term impact on other autoimmune diseases and may correlate with the specific pattern of B-cell tolerance defect in rrMS compared to other autoimmune diseases. Indeed, a subset of patients with rrMS display a proper removal of developing autoreactive B cells in the bone marrow, whereas this central B cell tolerance checkpoint is impaired in all other autoimmune diseases. To determine the impact of short-term anti-B cell therapy in rrMS on autoreactive B cell selection, we analyzed the frequencies of autoreactive new emigrant/transitional and mature naïve B cells before and after two courses of ocrelizumab anti-CD20 antibody injection in seven patients with rrMS. We identified an impaired central B-cell tolerance in four rrMS, three of which have already relapsed. In contrast, the other three rrMS patients displayed low frequencies of autoreactive B cells.
exiting the bone marrow and none have yet relapsed. Strikingly, anti-B cell therapy restored the impaired peripheral selection of autoreactive B cells in the three patients who displayed a functional central B-cell tolerance, whereas autoreactive B cells accumulated after anti-B cell therapy in the mature naïve B cell compartment of the four rrMS patients with defective central B-cell tolerance. Hence, rrMS is a heterogeneous disease that can be stratified into two distinct entities based on specific pattern of early B-cell tolerance defects and the efficacy of B-cell depleting therapy is associated with a normal central B-cell tolerance and the elimination of autoreactive B- and T-cells.

7) Farhana Rahman, Postdoc, Immunology & Rheumatology

Title: Deciphering CXCL4-mediated inhibition of TLR9 tolerogenic function in B cells

Abstract: CXCL4, also known as platelet factor 4, was found elevated in the serum of patients with systemic sclerosis (SSc) or systemic lupus erythematosus (SLE) but its involvement in the pathogenesis of these autoimmune syndromes remained unknown. A study from our lab recently showed that CXCL4 inhibits TLR9 function in B cells by sequestering TLR9 ligand CpG away from the late endosomal compartments where this receptor resides and abrogates central B cell tolerance, resulting in the production of autoreactive B cells. We now report that CXCL4 sequesters CpG in RAB5+ early endosomes from which TLR9 does not signal in B cells. We have also identified integrin V3, which binds CXCL4, as the receptor mediating CXCL4-dependent TLR9 inhibition in B cells. Indeed, we found that anti-integrin V3 prevents CpG intracellular mislocalization in the presence of CXCL4 in both BJAB and Ramos cell lines as well as in B cells from healthy donors. CXCL4-induced alterations in CpG intracellular trafficking are also corrected by SFK/SYK inhibitors, which suggests that integrin V3 signaling via SRC/SYK kinases play an important role in CXCL4-dependent TLR9 inhibition likely by activating LC3 recruitment to early endosomes. In addition, we observed that B cells from patients with SSc display a spontaneous altered CpG intracellular trafficking reminiscent of previous exposure to CXCL4 and that incubation with anti-integrin V3 restores proper CpG localization to RAB7+ late endosomes and enhances TLR9 responses in patient’s B cells. Hence, blocking integrin V3 may represent a novel therapeutic strategy to correct the impaired TLR9 tolerogenic function in SSc and other autoimmune diseases such as SLE, and prevent both the production of autoreactive B cells and the secretion of autoantibodies in these patients.
8) Alma Cepika, Faculty, Pediatric Stem Cell Transplantation and Regenerative Medicine

Title: Epigenetic signature and key transcriptional regulators of human antigen-specific type 1 regulatory T cells

Abstract: Our lab identified a defect in second messenger signaling downstream of the Treg IL-2R in allergy and autoimmune disease patients. Here we show that combination treatment using low dose IL-2 combined with a neddylation activating enzyme inhibitor (MLN4924 or TAS4464) was able to restore Treg function. Studies in vitro showed that combination treatment allowed prolonged maintenance of pSTAT5 activity in mouse and human Tregs compared to low dose IL-2 alone. Combination therapy also reduced the incidence of hyperglycemia in non-obese diabetic mice and prevented the development of asthma in the cockroach antigen induced model of asthma.

9) Fangyuan Wang, Visiting Instructor, Immunology and Rheumatology

Title: Restoration of Treg function using a combination of IL-2 and an inhibitor of neddylation

Abstract: Our lab identified a defect in second messenger signaling downstream of the Treg IL-2R in allergy and autoimmune disease patients. Here we show that combination treatment using low dose IL-2 combined with a neddylation activating enzyme inhibitor (MLN4924 or TAS4464) was able to restore Treg function. Studies in vitro showed that combination treatment allowed prolonged maintenance of pSTAT5 activity in mouse and human Tregs compared to low dose IL-2 alone. Combination therapy also reduced the incidence of hyperglycemia in non-obese diabetic mice and prevented the development of asthma in the cockroach antigen induced model of asthma.

10) Maka Gegenava, Guest, Rheumatology

Title: Role of advanced echocardiographic technique in the assessment of heart failure in patients with Systemic lupus erythematosus.
11) Daniel Fernandez, Staff, Chem-H

Title: MSKC - Stanford Shared Center for BioResearch

Abstract: The Stanford Sarafan ChEM-H Macromolecular Structure Knowledge Center (MSKC) trains researchers to run experiments in all aspects of biological research regardless of scientific background. MSKC provides state-of-the-art equipment and expertise for the production and purification and biophysical and structural characterization of biological macromolecules and their complexes with ligands, inhibitors, and partner proteins. Here it is you who perform experiments - as a MSKC lab member you are expected to get your “hands dirty” at the wet bench. Fostering interdisciplinary research, the MSKC staff provide training and guidance in a friendly and inclusive environment.

12) John Pluvinage, Resident Physician, UCSF, Neurology

Title: ABCD: Autoimmune B12 Central Deficiency

Abstract: Vitamin B12 is critical for hematopoiesis and myelination.1 Deficiency can cause neurologic deficits including loss of coordination, spasticity, and cognitive decline.2,3,4 However, diagnosis relies on vitamin B12 measurement in the blood which may not accurately reflect levels in the brain. Here, we discovered an autoimmune cause of vitamin B12 deficiency restricted to the central nervous system (CNS), termed autoimmune B12 central deficiency (ABCD). Using programmable phage display, we identified an autoantibody targeting the transcobalamin receptor (CD320) in a patient with progressive tremor, ataxia, and scanning speech. Patient immunoglobulins impaired cellular uptake of vitamin B12 in vitro. Despite normal serum levels, vitamin B12 was nearly undetectable in her cerebrospinal fluid (CSF). Immunosuppressive treatment and high-dose systemic vitamin B12 supplementation were associated with increased CSF B12 levels and clinical improvement. Autoantibodies targeting the same epitope of CD320 were identified in 7 other patients with neurologic deficits of unknown etiology and in 6 percent of healthy controls. In 132 paired serum and CSF samples, detection of anti-CD320 in the blood predicted B12 deficiency in the brain. These findings elucidate a new autoimmune cause of metabolic neurologic disease that may be amenable to immunomodulatory treatment and/or nutritional supplementation.

13) Willemijn van Deursen, Graduate Student, Medicine

Title: Mouse Spleen Organoid as a stimulatable model for de novo ligand discovery

Abstract: Ly49 receptors, which are ubiquitously expressed on Natural Killer (NK) cells, have been identified as unique surface markers for a regulatory CD8+ T cell subset in
mice. These Ly49+CD8+ T cells, and their human functional equivalent KIR+CD8+ T
cells, have demonstrated immunoregulatory activity in various autoimmune diseases,
including multiple sclerosis and systemic lupus erythematosus. One particular Ly49
receptor variant, Ly49F, is highly expressed on CD8+ T cells but lowly expressed on NK
cells. Given this selective expression, it may play an important role in the
activation/inhibition of the Ly49+CD8+ T cells of interest. We expressed a biotinylated
version of the extracellular domain of the Ly49F protein in a mammalian expression
system. We assembled the purified protein into tetramers and spheromers (12-pMHC
multimer) for use as a staining reagent. We cultured novel mouse spleen organoids for
up to 14 days under various stimulation conditions and stained with our Ly49F multimer
reagent along with other cell surface markers. We found that the Ly49F tetramer and
spheromer cleanly stain ~1% of CD4+ T cells on day 7 under stimulation with cGAMP or
CD3/CD28. This demonstrates the mouse spleen organoid as a tool that can be
optimized for bottom-up cell phenotyping for ligand discovery and provides a vital clue
into the mechanism regulating Ly49+CD8+ T cells.

14) Dinara Bogetic, Staff, Pathology

Title: Food Insecurity Mitigation in Food-Allergic Children Using Food
Prescription Intervention

Abstract: Food insecurity disproportionately affects approximately 23% of the US
population. Food-insecure families managing food allergies encounter additional
challenges in accessing safe food. During the COVID-19 pandemic food insecurity
increased 6-fold, adversely impacting families managing food allergy.

15) Reyna Sharma, Clinical Research, Sean Parker Center

Title: 'The Effect of Persistent Gastrointestinal Symptoms during Cashew Oral
Immunotherapy on Participant Outcomes

Abstract: Food allergies pose a significant health concern and oral immunotherapy
(OIT) has emerged as an effective treatment option. However, the presence of
persistent gastrointestinal symptoms (PGIS) during OIT raises concerns about its effect
on participant outcomes such as achieving study completion and withdrawal rates.