Problem Set 2 – Immunology – Spring 2026

Do not use AI in preparing your answers (e.g., ChatGPT or any similar LLM).

1. **Based on Dr. Alexander Rudensky's lecture (submitted by Joshua Lau):**

Specific Human Leukocyte Antigens (HLA) alleles are associated with increased rates of autoimmune disease (approx 1 page).

1. Suggest a mechanism / hypothesis by which an HLA allele may contribute to Autoimmunity

2. Design a strategy / series of strategies to experimentally confirm this mechanism, including
   a. 1. Experimental outline
   b. 2. Key controls
   c. 3. Expected results if your mechanism is true

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2. From Dr. Gabrielle Rizzuto:

In class, we discussed 3 exceptional circumstances where failure of fetomaternal tolerance leads to poor pregnancy outcomes. One of these, Hemolytic Disease of the Fetus and Newborn (HDFN, also known as "Rh disease"), used to affect approximately 1% of pregnancies prior to the development of a successful prophylactic therapy in the 1960s. Despite the success of this therapeutic, many unanswered, interesting questions remain about mechanism of disease and why the therapeutic works. Please help us figure out some answers!

1. Summarize the pathogenesis of Rh disease.

    a. Curiously, even prior to 1960, only 16% of $RhD^{negative}$ females developed clinically significant RhD-specific IgG in pregnancies where the fetus was RhD^{+}. Speculate on the rarity of sensitization here (i.e. state a logical hypothesis for why maternal antibody responses only occur in a minority of at-risk pregnancies). Please design an experiment to test your hypothesis.

2. Administration of two doses of polyclonal RhD-specific IgG (derived from sera of immunized donors; first dose at 28 weeks and 2^{nd} dose immediately after delivery) successfully prevents the generation of maternal RhD-specific IgG in at risk pregnancies. Despite the success of this decades-old therapeutic, mechanisms for *how* it works remains unclear. Please comment on a possible mechanism. Then, design an experiment (or series of experiments) to test this a hypothesis driven approach.

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3. Based on Dr. Tobias Hohl's lecture (Submitted by Ecenur Turkay):

A bacterial pathogen expresses a surface protein, **protein X,** which is hypothesized to help the bacteria evade the host immune system.

It is hypothesized that the **X protein might help the bacteria evade complement-mediated killing through Factor H recruitment**. Focus on **how you would approach the experiment and think through the logic**, without getting into the technical details of specific assays or reagents.

- **Experimental design:** What strains, conditions, or manipulations could you use to test whether protein X is responsible for complement evasion?
- **Readouts:** How would you measure whether Factor H is recruited, complement activity is altered, and bacterial survival is affected?
- **Controls:** What types of conditions would help you interpret results and ensure conclusions are specific to protein X-mediated Factor H recruitment?
- **Interpretation:** How would different outcomes indicate whether protein X protects bacteria through Factor H recruitment?

Note: Aim for a concise, well-reasoned response. Try to keep it under 500 words, with around 400 words being ideal.

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4. From Dr Ivan Kotchetkov:

You are part of a team designing a CAR T cell therapy clinical trial for the most common primary malignant brain tumor, glioblastoma. Your CAR construct targets the antigen CD70 and constitutively expresses the glucose transporter, GLUT1, to give it a competitive advantage in the low-glucose brain tumor environment. The CAR T cell product is delivered as a single dose intraventricularly. You collect samples of tumor before and after treatment as well as CSF and blood at baseline and longitudinally after treatment. Propose an analysis plan for the correlative samples that will help you generate hypotheses about mechanisms of response and resistance to therapy. The plan should specificy controls and comparisons that will give you insight into how to prioritize hits in what would otherwise be descriptive data.

You find that in your serial sampling, you detect much lower levels of the CAR construct in the CSF after 2 weeks, but it is still there. Propose 2 hypotheses for what might be happening and how you might test them using the samples and pre-clinical models to establish the mechanism.

You have completed your analysis of the correlative samples and found significant enrichment of CAR T cells expressing the chemokine receptor CXCR3 in tumor and cerebrospinal fluid compared to blood. Higher CXCR3 expression is also correlated with improved clinical responses. 1) Propose a set of experiments to determine whether this is a biologically relevant molecule. 2) If your experiments validate its importance, how would you incorporate this finding into your next clinical product?

Distribute: March 2, 2026 Due: March 16, 2026, 3:00 PM via email to David McDonagh

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5. From Dr Yaprak Ozakman's lecture:

1. Tuberculosis (TB) and cancer both involve chronic immune pressure and structured immune niches (granulomas vs tumors).

Briefly describe:

a. What it means for the immune system to "contain but not eliminate" a threat.
b. How granulomas in TB and tumors in cancer represent similar biological strategies.
c. One advantage and one cost of immune containment.

2. BCG is effective in preventing severe TB in children and is used to treat bladder cancer, yet it does not reliably prevent adult pulmonary TB. Using ideas from the lecture (containment, persistence, structured niches, immune equilibrium), propose:
   a. One biological explanation for this paradox.
   b. One experiment to test your explanation.

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6. From Dr Mariia Akhmanova's lecture:

Choose one of the following assignments:

1. Which immune cells exhibit the highest *in vivo* migration speeds? Describe the specific modes of force transmission they utilize to navigate diverse tissue architectures and explain how these mechanisms adapt to the physical properties of their environment.

2. Categorize the physical barriers that migrating cells encounter *in vivo*. Propose specific mechanisms that cells employ to penetrate these obstacles.

3. You are provided with an unlabeled vial of cells. Devise a comprehensive set of *in vitro* experiments to characterize their migratory capabilities. Based solely on the results of these experiments, is it possible to conclusively identify the specific immune cell type? You have unrestricted access to all standard laboratory reagents and imaging equipment.

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