



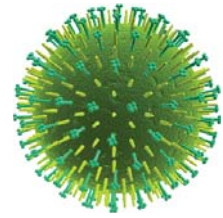
# CASE TEACHING NOTES

for

## “Immunological Malfunction?”

by

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### INTRODUCTION / BACKGROUND

This problem-based case study begins with a young couple trying to understand the cause of their infant boy's constant bacterial infections. As students work through the case study, they review some basics of immunology. The couple's physician then presents the results of blood and genetic testing, and a genetic counselor helps the family understand the implications of X-linked agammaglobulinemia with hyper-IgM syndrome. Students must then analyze how a mutated ligand for the CD40 receptor can prevent the crosstalk between T and B cells necessary for isotype switching and how this leads to a compromised immune response. Also considered are implications for other family members, the treatments for this condition (immunoglobulin therapy) and cure options for the couple's son (cord blood stem cell transplant/ bone marrow transplant).

X-linked agammaglobulinemia with hyper-IgM syndrome is a rare disease that usually presents during the first year of a male's life with recurrent bacterial infections. Children are often diagnosed after a bout of *Pneumocystis carinii* pneumonia, a fungal infection that normally affects only individuals with compromised immune systems. The genetic defect underlying this syndrome is due to a mutation in the gene for the CD40 ligand found on activated T cells. The CD40 ligand (CD40L) binds to the CD40 receptor on B cells and is responsible for triggering IgE secretion and isotype switching of IgM to IgG and IgA. Therefore, patients with this mutation present with very low (or absent) levels of IgG, IgA and IgE and normal to above average levels of IgM and IgD. Once diagnosed, the patient must receive immunoglobulin transfusions every three to four weeks for life. A permanent cure is possible if the patient can receive an HLA matched bone marrow transplant or cord blood stem cell transplantation.

This case was developed for use in the second semester of Human Anatomy and Physiology to complement study of the immune system and to emphasize the crosstalk that occurs at the cellular level between B and T cells for proper immune system function.

### Objectives

- Students finishing this case will have reviewed the different classes of antibodies and their specific functions. They will also review the concept that the different classes of antibodies arise through isotype switching (switching the heavy chain type).
- Students will also apply their knowledge of basic genetics by reviewing how X-linked disorders are passed along and will be introduced to (or reminded of) the role of genetic counselors in medicine.
- By studying the role of CD40L in the immune system, students will delve a bit deeper into immunology than they would in a general Human Anatomy and Physiology course and thereby (hopefully) appreciate how the knowledge they are acquiring can be applied. Furthermore, the importance of crosstalk between B and T cells will be emphasized.
- Students will also look into how immunoglobulin therapy can help patients with an immunodeficiency

disease. They will also realize that it is only a treatment, not a cure. This will lead into a discussion of the potential of biotechnology to find a cure and stimulate discussion of science and ethics.

## CLASSROOM MANAGEMENT

Students are presented with the case study at the time that the immunological system is being studied. My class uses an online discussion forum to work with each other to find the answers to the questions presented. This is done so that I can determine if all students are participating and to what degree. It also allows students to share resources, suggest answers, and work together to find the solution. Finally, the online forum preparation ensures better classroom participation and discussion on the day that the case study is reviewed. The structure of the case scenario and questions could be presented to the class as an interrupted case that is delivered and completed entirely online.

I review the basics of the case by first writing down Daniel's symptoms. We then address the study questions as we work through the case keeping a list of answers on the board. I find that writing down the different pathways that antigens take to stimulate both B and T cells and how they later interact is a key portion of this exercise. This crosstalk between cellular mediated immunity is one of the main points I wish to make as students often find it difficult to visualize how B and T cells interact.

We then discuss Daniel's current therapy and why it may or may not be the best solution. I like to end the class with a discussion about the application of biotechnology to this disease with questions such as: What is gene therapy? What is prenatal testing? What is *in vitro* fertilization and pre-implantation testing? What are the scientific ethics that may apply here?

I do not collect answers to the questions, but instead expect students to participate in our online forum and to be able to answer short answer questions regarding the case and topics discussed during class on the next exam.

## ANSWER KEY

Answers to the questions posed in the case study are provided in a separate answer key to the case. Those answers are password-protected. To access the answers for this case, go to [the key](#). You will be prompted for a username and password. If you have not yet registered with us, you can see whether you are eligible for an account by reviewing our [password policy and then apply online](#) or write to [answerkey@sciencecases.org](mailto:answerkey@sciencecases.org).

## CLOSURE

Susan and Joe now know what is wrong with their son. Daniel has a mutation in the gene for the CD40 Ligand that is present on the surface of T cells. Without a working version of this gene, T cells cannot bind to the CD40 receptor on B cells in order to stimulate secretion of IgE and isotype switching (immunoglobulin heavy chain switching) to produce IgG and IgA. Therefore, Daniel can only make IgM (and IgD). The treatment is to provide immunoglobulin via transfusions every 3–4 weeks in order to provide the missing classes of antibodies. Hopefully, the presence of normal levels of IgG in Daniel's bloodstream after transfusion will encounter and immobilize/destroy foreign antigens thereby decreasing the amount of IgM that Daniel's body is producing in response to foreign antigens (his immune system's only option).

However, by the age of 25, boys with this disease will often exhibit liver disease and malignancy (there are also several other potential complications, see references). Susan and Joe know that their only hope for a permanent cure at the moment is to perform a bone marrow transplant or a cord blood stem cell transplant in order to provide Daniel with stem cells that produce fully functional (normal CD40L) T cells. Their best option is to provide a matching HLA sibling for Daniel. They can undergo prenatal screening to determine

if the fetus also contains a mutated copy of the CD40L gene. They could also opt for *in vitro* fertilization with genetic testing of the blastocyst(s) prior to implantation for both mutated CD40L and/or matching HLA. Both of these options carry risks and can stimulate discussions about science and ethics.

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