MASTER'S RESEARCH PROJECT PROPOSAL

O Death Where Is Thy Sting? Immunologic Tolerance To Apoptotic Self

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KEYWORDS

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune system that causes patients' immune systems to attack healthy tissue. Current therapeutic treatments are limited, but researchers are making new discoveries in an effort to de-mystify this disease and create new treatments. These scientists have a need to communicate their findings to a variety of audiences, including potential graduate students and future researchers. Thus, my project aims to fulfill these needs for Dr. Tracy McGaha at the Princess Margaret Cancer Centre. I will be creating a 3D animation on the newly-discovered role of the aryl hydrocarbon receptor (AhR) in SLE, while implementing good design and storytelling principles found through a literature review and media audit. Ultimately, this animation will hopefully be able to communicate the topic effectively to a many audiences and stimulate interest in the field.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system attacks healthy tissue in various parts of the body. It's estimated that 5 million people worldwide suffer from a form of SLE, but our current understanding of the mechanisms that cause this disease is poor (Roper, 2012). This is because the disease is very multifactorial, and patients with SLE display a wide variety of symptoms and organ involvement as well as diverse autoantibodies. As such, current therapeutic treatments are few and there is a great need for new medications and therapies to aid suffering patients (Tsokos, Lo, Reis, & Sullivan, 2016). Fortunately, research in the field is making great progress. Current research is especially focused on how the everyday process of cell apoptosis can lead to development of systemic autoimmunity.

Research labs depend on effectively communicating their work to attract new talent as well as publicity and funding. Therefore, they need ways to communicate new and innovative research to a wide variety of audiences such as potential graduate students, other researchers, and the general public. Animation is one effective and accessible way to both educate and interest these audiences, integrating visual and auditory elements with storytelling. For my project, I aim to foster interest in lupus research, and specifically the research being done by my content advisor Dr. Tracy McGaha at the Princess Margaret Cancer Centre, by creating an animation for the McGaha lab's website in partnership with the University of Toronto Department of Immunology.

BACKGROUND

Cell apoptosis and SLE

The connection between cell apoptosis and the development of system autoimmunity is well-established. Normally, efferocytosis (apoptotic cell phagocytosis) is accompanied by an immunologically

silent cell death. The definition of immunologically silent cell death includes recognition of apoptosis by various cell receptors; production of anti-inflammation effector molecules (such as IL-10 and TGF- β), inhibiting recruitment of macrophages and decreasing secretion of pro-inflammatory cytokines; and acquisition, by dendritic cells and macrophages, of a tolerogenic phenotype and long-term adaptive immune tolerance to apoptotic cell-associated antigens (Mahajan, Herrmann, & Muñoz, 2016; McGaha & Karlsson, 2016). All of this means that efferocytosis is usually not accompanied by inflammatory signals.

Genetic deletion experiments in mice show that alteration or loss of pathways related to the process of recognition and clearance of apoptotic cells leads to inflammation and autoimmunity (McGaha & Karlsson, 2016). During apoptosis, a cell forms apoptotic bodies through cell breakup into multiple vesicles. These apoptotic bodies contain modified cell-derived material, a source of nuclear autoantigens. If clearance of apoptotic bodies is inadequate, leakage of cytoplasmic and nuclear autoantigens (like ribonucleoproteins, DNA, and histones) into extracellular space may lead to production of autoantibodies and opsonization (intake) of intracellular autoantigens by immune cells. This process then triggers the secretion of pro-inflammatory cytokines. As a result, efferocytosis can stimulate classic inflammatory processes in the immune system and lead to development of systemic autoimmunity (Podolska, Biermann, Maueröder, Hahn, & Herrmann, 2015).

Shinde et al. (2018) point to the aryl hydrocarbon receptor (AhR) as an important player behind SLE. AhR is a receptor and transcription factor activated by TLR9 (toll-like receptor 9), a protein that binds to nucleic acids. In mice macrophages and dendritic cells, TLR9 recognizes DNA from apoptotic cells and activates AhR. AhR then translocates from a chaperone complex in the cytoplasm to the nucleus, stimulating production of anti-inflammatory cytokine IL-10. In conclusion, AhR plays an important role in immunologically silent cell death by suppressing inflammatory immunity toward apoptotic cells. While this is an exciting discovery, there is still much more research to be done before researchers are able to utilize their findings towards making new treatments for SLE. This is where scientific visualizations can step in to generate interest in the field from students and funders.

Advantages of using animation for scientific education

Animations have been shown as effective visualization tools to both educate and interest audiences. For one, they can increase long-term retention of a scientific topic compared to static visualizations (O'Day, 2007). In a study conducted by Stith (2004), a university lecture was given on apoptosis, after which a subsection of students were shown a 65-second animation on the lecture topic. When those students were brought back and the whole class was given a test, students who watched the animation scored 14% higher than those who didn't. In another study by McClean et al. (2005), students attempted to learn about protein synthesis through combining various permutations of individual study, formal lecture, and viewing of a three-dimensional animation. Students that viewed the animation scored significantly higher in follow-up tests than students who didn't in all cases.

Some reasons that animations may be particularly useful in education of molecular processes is that they are effective in visualizing spatial and dynamic processes (Tibell & Rundgren, 2010) and they can help convey a process without oversimplification (Iwasa, 2010). Also, animated graphics are more likely to increase emotional interest in a topic than static graphics because animation tends to induce higher

arousal levels in the viewer (Kim, Yoon, Whang, Tversky, & Morrison, 2007). For these reasons, animations have been increasingly used to summarize and contextualize specific research findings on journal and research websites (Iwasa, 2010). Because animation has been shown as a valuable tool to teach complex cellular molecular topics, it will be an effective medium to explain the technically-difficult research of my content advisor.

Media Audit

To gain a better understanding of effective and ineffective elements in molecular animations, I analyzed various animations that are related in some way to my project. There are no animations or illustrations on the specific topic I will be covering, so examining related visualizations is a useful method to explore possible techniques I can employ in my own project.

Figure 1. “Systemic Lupus Erythematosus” (“Systemic Lupus Erythematosus,” 2016)

One video created by Random42 Scientific Communication, titled “Systemic Lupus Erythematosus,” is an animation on SLE for pharmaceutical client AstraZeneca (“Systemic Lupus Erythematosus,” 2016). It focuses on Type 1 interferons as a drug target and its target audiences are doctors and health care professionals. In terms of the background information it offers on SLE and the depth and complexity of content, the animation is similar to the one I plan to produce. It is a very professionally-made video with colorful and dynamic visuals that attract attention; it fully takes advantage of the animation medium’s ability to increase emotional interest and arousal levels of audiences (Kim et al., 2007). While components like flashy colors and dramatic music can engage audiences, however, extraneous material or information can also detract from the piece’s effectiveness at communication (Mayer & Moreno, 2002). In this particular video, the music drowns out the narration at times. When creating visualizations that must both educate and appeal to audiences, one must find an ideal amount of extraneous, “flashy” material to include such that it doesn’t overwhelm the rest of the work.

Figure 2. “Molecular Animation of Cell Death Mediated by the Fas Pathway” (Berry, 2007)

Next, an animation titled “Molecular Animation of Cell Death Mediated by the Fas Pathway” describes a pathway behind apoptosis (Berry, 2007). It was made to accompany a research paper, similar to how my animation will largely focus on the findings of one paper, and so its target audiences are researchers and advanced biology students. The animation makes effective use of the immersive camera metaphor at the molecular level; this camera style, in which the camera seems to be immersed inside the cellular environment, is able to show depth of field at the expense of molecular concentration and is better for visualizing binding and dissociation of components. The immersive camera metaphor is contrasted with the cross-section camera metaphor, which shows a cellular environment as a cross-section and is better able to show molecular crowding at the expense of depth perception (McGill, 2008). However, while camera use is appropriate at the molecular level, its use is odd at the cellular level where the displayed cells’ location in the body is unclear. Also, the animation lacks narration, which increases the cognitive load of viewers who must read labels instead. The dual-channel assumption describes how humans have separate channels to process visual and auditory representations. Therefore, it’s better to take advantage of both channels by, for example, employing visual images combined with auditory narration as opposed to visual images with visual text. Also, the spatial contiguity principle states that viewers learn better when on-screen text is next to relevant imagery; otherwise, viewers waste cognitive capacity searching for text (Mayer & Moreno, 2002). In this particular animation, the labels in this animation are often far from the event center. In conclusion, effective educational animations utilize both appropriate visualizations and accompanying narration.

“Transcriptional Activation of the AhR” is a molecular animation on the AhR molecule, which I will visualize in my project (Koch & Harper, 2006). Its target audiences are advanced biology students and researchers. At the start of the video, the different actors are effectively introduced one by one to the audience, allowing those with less advanced scientific training to follow along. The apprehension principle advises visual creators to keep content to the education level of the audience (O’Day, 2008). When communicating to multiple audiences, one should provide additional details in a way that does not distract (Johnson & Hertig, 2014). When communicating to scientists, ancillary information can be reduced or removed, but by displaying introductory information in a concise and structured manner, this animation is able to broaden its reach.

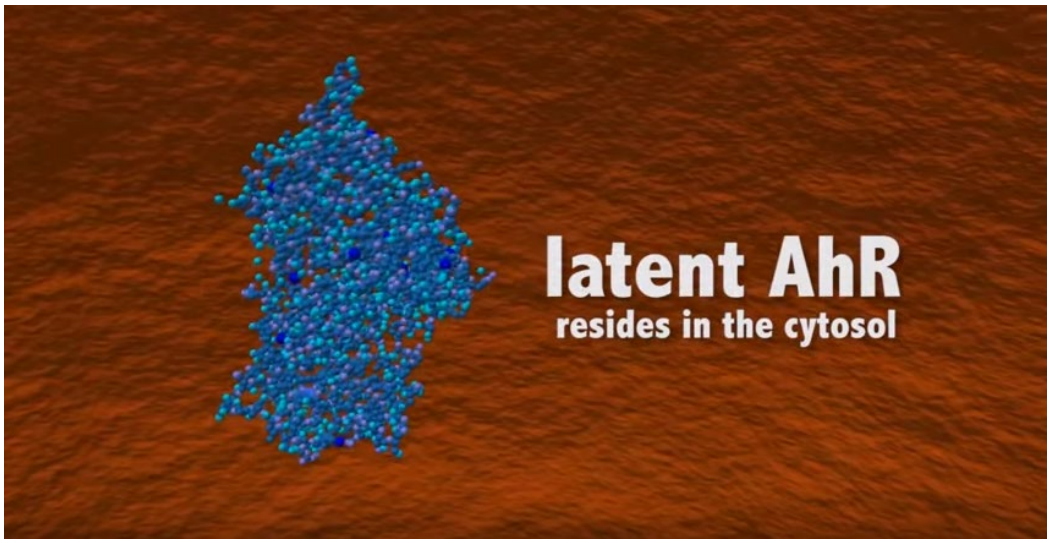

Figure 3. “Transcriptional Activation of the AhR” (Koch & Harper, 2006)

In terms of molecular visual treatment, the video uses only spherical atoms to represent its molecules. While this approach is effective with scientists who understand abstract representations of a phenomenon, students are more constrained by a representation’s superficial features (Tibell & Rundgren, 2010). Therefore, the video might be made more effective for students by using surface representations of molecules. Other issues with this animation include fast narration, quickly disappearing text, and text that does not match the narration. All these aspects increase the cognitive load placed on viewers as described previously.

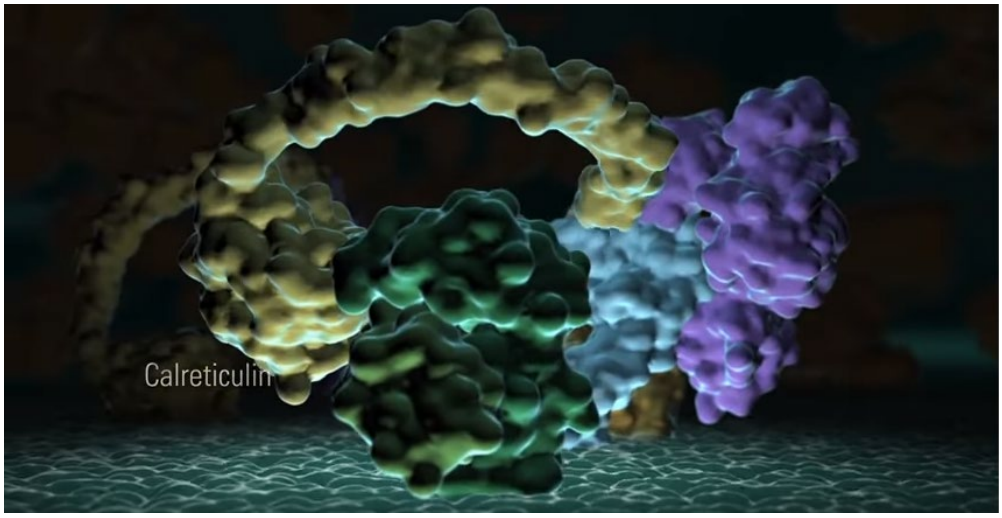

Figure 4. “Class One Molecules of the Major Histocompatibility Complex”

Lastly, “Class One Molecules of the Major Histocompatibility Complex” is an animation on an immunological topic created by a Biomedical Communications student as a Master’s Research Project (Accorsi, 2011). It explains to biology and immunology students how class one molecules of the major histocompatibility complex are assembled. The video successfully employs visual cues, such as changes

in lighting, saturation, and color, to direct viewer attention during the complex processes that occur. Visual cues in animations can help learners comprehend complex dynamic processes (de Koning, Tabbers, Rikers, & Paas, 2007). Spotlight cues, which this animation uses effectively, should be used to determine when and in what order elements of the animation should be paid attention to (de Koning, Tabbers, Rikers, & Paas, 2010). While the video utilizes techniques such as visual cues to improve learning comprehension, there are still many difficulties associated with teaching long and complex processes to students. There is a sequence in the middle of this animation, one explaining the assembly of class one molecules in the ER lumen, that has little visual variability; the camera circles the complex of molecules as each of the many steps of assembly is explain and shown. The complex sequential steps, consistent visual palette, and heavy narration of this section may cause some viewers to have difficulty paying attention or following along. The creator does use dramatic lighting, camera movements from one complex of molecules to another, and music to help retain interest and arousal in viewers. The animation is achieves its educational goals, but attracting and keeping viewer attention and interest is a specific challenge for scientific animations that I will have to keep in mind.

Overall, there are various methods to successfully using animations to convey complex molecular topics. Structured introductions of molecular characters, clear narration, and vibrant visuals help an animation to reach various audiences. An immersive camera and visual cues help to tell a story accurately and dynamically. My project will fulfill the need for a visualization on the latest SLE research findings that incorporates the principles of good animation discussed here. During the creative process, I will also tackle discussed challenges such as explaining complex processes while retaining viewer interest and reaching a broad audience.

AIMS AND OBJECTIVES

Goal of the project: To attract interest from prospective graduate students and postdocs, the scientific community, and the science-savvy public about new research concerning a pathway behind development of SLE.

Objectives

1. To create a 3D animation geared primarily towards prospective graduate students and postdocs for the McGaha lab's website, explaining current and innovative researching findings in an interesting and attractive manner.
2. Secondarily, to create an animation that may also be used, whether as a whole or as a part, in research conferences aimed at the scientific and medical community.
3. Secondarily, to create an animation that members of the science-savvy public may take interest in.
4. To investigate what design principles and storytelling techniques are most effective for creating a clear, engaging scientific animation able to educate and interest a variety of audiences with differing levels of background knowledge.

METHODS

I will be creating a 4 to 5 minute 3D animation targeting primarily prospective graduate students interested in immunology. The animation may also secondarily communicate to the scientific community and science-savvy public.

Throughout the whole creative process, I will keep in mind and apply the effective animation techniques that I have discussed in this paper. In terms of storytelling, content, and visual treatment, I will aim to create a flexible animation that is able to educate and interest many audiences. For example, I will start with an introduction on SLE and concisely inform audiences on the background knowledge needed to understand the main topic. I will employ an immersive camera to best show the interactions of the protein actors. The style of the 3D animation should stimulate attention in viewers through color, visual cues, dynamic motion, and sound effects. However, I will also keep in mind not to let the attention-grabbing elements become overwhelming and overpower the learning experience.

Within the animating process, the script will assume that the audience has intermediate knowledge of biology. I will consult my content advisor and faculty for opinions on content, accuracy, and flow. The next stage is creation of a storyboard, which will be improved upon iteratively based on feedback, and then formation of an animatic, which is an animated adaptation of the final storyboard. 3D assets will then be modeled and assembled in to an animation in Autodesk Maya.

Evaluation for success will be based on the approval of my content advisor, Dr. McGaha, and whether the animation meets his needs and expectations. The animation will primarily be displayed on Dr. McGaha's website and secondarily at possible research conferences.

ANTICIPATED SIGNIFICANCE

This project will explore effective ways to design an engaging, educational, and accurate animation aimed at audiences of varying educational levels on a complex scientific topic. For the target audience, this animation will fulfill the need for a visualization on new SLE research findings. The audience will be able to learn about the current understanding of SLE causative mechanisms as well as innovative research being done in the McGaha lab. For Dr. McGaha as a content advisor, this animation will allow him to explain his research in an exciting and dynamic format to various audiences, hopefully leading to increased attention from students, scientists, and the public. Ultimately, this animation may help fuel interest in SLE and the important research being done to develop treatments for people who suffer from this debilitating disease.

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