

## Activity 6: Chimeric Botulinum Toxin Therapeutics

### Assignment: Writing and Reviewing Grant Proposals

Botulinum toxin paralyzes muscles and can lead to death if not treated. However, if diluted or engineered, it can be used for medicinal purposes and has already been recruited for a variety of therapeutic uses. Diseases that can benefit from botulinum administration include those that involve muscle spasticity and chronic pain. Recently, recombinant forms of many bacterial toxins have been fused to proteins that normally recognize aberrant cells and trigger cell death. These protein chimeras have been touted to have great potential for treating a multitude of cancers and endocrine disorders. Not surprisingly, a number of biotechnology companies have jumped on the fusion toxin bandwagon and are competing for market share.

In this activity, you will play the roles of two characters: first, a scientist from a biotechnology company proposing a new chimeric botulinum toxin therapy and, then, a member of a scientific advisory board reviewing proposals of your peers.

#### Instructions

1. Complete the assigned reading and review the websites (suggestions for textbook readings may be found in the Teaching Notes to Activity 6).
2. Consider the situation outlined below. Play the role of the scientist and develop a proposal. Be sure to address the following:
  - Briefly review the economic and health benefits of constructing a chimera.
  - Outline the experiments you would execute to develop a chimera to the disease of your choice.
  - Describe how you would test the efficacy and safety of the chimera.
3. The proposal should also address the questions found at the end of this assignment.
4. Exchange your proposal with a peer.
5. Play the role of the scientific advisory board member and critique your peer's proposal using **Resource Five: Peer Assessment of Writing**. In this critique, be sure to do the following:
  - Include a set of questions for the scientist.
  - Uncover potential pitfalls in the proposal that include both scientific and economic perspectives.
  - Suggest alternative chimeras that might alleviate these pitfalls.
6. Turn in a portfolio of your work that includes the first version, the peer-review and the revised version of your proposal for a grade.

#### The Situation

1. A scientist at a new start up biotech company is presenting a proposal to the scientific advisory board of the company.
2. This proposal describes a set of experiments to construct and use a botulinum toxin chimera to treat a disease (you choose which one).
3. Many diseases might be treatable by new applications of botulinum toxin. Cancer is a leading cause of death in the U.S. and developed countries, while infectious diseases are more problematic in the developing world. Thus, treatments for cancer

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could lead to large revenues, while treatments or vaccines for infectious diseases may need to be subsidized by public health organizations or national governments.

### Questions

1. Which disease would you like to treat or prevent? What causes it? How can drugs treat the symptoms?
2. How does a chimera differ from conventional chemotherapy? What advantages does it offer? What risks might it carry?
3. What components will your chimera contain? How will it be made? What is the rationale?
4. How long does it take for a new drug to reach the general market—from development through testing? How much does it cost to bring a drug to market?
5. What guidelines and how many testing stages are required for researchers to obtain an NDA (New Drug Application)? Remember that the researchers need to bring an IND (Investigational New Drug) application to the FDA before they can even begin the process.
6. What would the experimental set-up be for the testing of the drug in animals? What about human clinical trials? Describe the target population, sample size, controls.
7. Would this drug be undergoing Phase IV trials or post-marketing surveillance? Explain your answer.

### Literature (reviews are indicated with \*\*)

1. Kiyatkin, N., A. B. Maksymowych, et al. (1997). "Induction of an immune response by oral administration of recombinant botulinum toxin." *Infection and Immunity* 65(11): 4586-91.  
<http://iai.asm.org>, and <http://iai.asm.org/cgi/reprint/65/11/4586.pdf>
2. Kreitman, R. J. (2000). "Immunotoxins." *Expert Opinion in Pharmacotherapy* 1(6): 1117-29. \*\*
3. Lacy, D. B. and R. C. Stevens (1998). "Unraveling the structures and modes of action of bacterial toxins." *Current Opinion in Structural Biology* 8(6): 778-84.
4. Liu, S., S. Netzel\_Arnett, et al. (2000). "Tumor cell-selective cytotoxicity of matrix metalloproteinase-activated anthrax toxin." *Cancer Research* 60(21): 6061-7.
5. Mendelsohn, J. and J. Baselga (2000). "The EGF receptor family as targets for cancer therapy." *Oncogene* 19(56): 6550-65.\*\*
6. Pastan, I. and D. FitzGerald (1991). "Recombinant toxins for cancer treatment." *Science* 254(5035): 1173-7.\*\*
7. Simpson, L. L. (2000). "Identification of the characteristics that underlie botulinum toxin potency: implications for designing novel drugs." *Biochimie* 82(9-10): 943-53.

### Websites

1. Simpson, L., N. Kiyatkin, et al. (1997). Compositions and methods for systemic delivery of oral vaccines and therapeutic agents. [Pharmcast.com](http://Pharmcast.com). U.S.A., Thomas Jefferson University (Philadelphia, PA). This site is a patent application filed by Simpson et al, for the development of oral vaccines that use botulinum toxin as a

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component.\*\*

[http://www.pharmcast.com/Patents/041800OG/6051239\\_Vaccines041800.htm](http://www.pharmcast.com/Patents/041800OG/6051239_Vaccines041800.htm)

2. Chamany K. (2000). “Public Health Issues for the 21<sup>st</sup> Century Seminar Series Web Site.” This site has links to many other sites for vaccine production, drug access, and clinical trials.\*\*

[http://www.lang.edu/sts/seminarseries/ID\\_Web/index.html](http://www.lang.edu/sts/seminarseries/ID_Web/index.html)

3. Pecoul B, Chirac P, Trouiller P, Pinel J. (1999). “Access to essential drugs in poor countries: a lost battle?” *JAMA* 281(4): 361-7.

<http://www.accessmed-msf.org/upload/ReportsandPublications/19920011135443/JAMA.pdf>

4. NCI. “Science Behind the News: Understanding the Immune System.” This site is a graphic slide show of immune mechanisms, immunotoxin therapy (slide 32), and genetic engineering for vaccine development.

<http://newscenter.cancer.gov/sciencebehind/immune/immune01.htm>

5. FDA. FDA Consumer: From Test Tube To Patient: New Drug Development in the United States. January, 1995.

[http://www.fda.gov/fdac/special/newdrug/ndd\\_toc.html](http://www.fda.gov/fdac/special/newdrug/ndd_toc.html)

6. Okonek, B; Peters, P. “Vaccines—How and Why?”

[http://www.accessexcellence.org/AE/AEC/CC/vaccines\\_how\\_why.html](http://www.accessexcellence.org/AE/AEC/CC/vaccines_how_why.html)