

# Maria, Metastasis, and Methotrexate

by

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## Part I – The Diagnosis

Maria walked out the medical office and slumped over the steering wheel of her car. She was right to have come in at the end of the workday to avoid returning to the office of the non-profit she ran afterwards. The biopsy confirmed her fear; it was breast cancer. Now the doctor wanted her to come in for more scans to determine whether the cancer had spread anywhere else in her body. Questions raced through her mind and tears welled up in her eyes. How could this happen? What was she going to do next? Could the doctor help her?

She raised her head after a few minutes, catching her reflection in the rearview mirror. *I'm only 43... I have decades of life ahead of me!*, she thought. She was determined to do everything she could, learn about her options, and work with her care team to beat cancer.

### Questions

1. Maria's doctor is worried her cancer may be metastatic, meaning it could have spread from the breast tissue to other parts of the body. Normal, non-cancerous breast tissue cells experience anchorage dependence and density-dependent inhibition. Loss of these limitations on cell growth is a hallmark of cancer. Explain each of these terms.
  - a. Anchorage dependence:
  
  
  
  
  
  
  
  
  
  
  - b. Density-dependent inhibition:
  
2. How would the loss of anchorage dependence allow for metastasis to occur?

## Part II – The Treatment

A few weeks after receiving the news, Maria met with her doctor again to discuss the results of her additional tests. At some point, the cancer had spread from her left breast. The scans revealed another small tumor on her liver. Despite the fear that came with the diagnosis of metastatic cancer, her doctor tried to reassure her. Dr. Lee explained that treatments for metastatic cancer were first developed in the 1950s and had been improving every year since then. She recommended that Maria undergo a rigorous chemotherapy regime that included the use of the drug methotrexate, the first drug ever shown to successfully treat metastatic cancer, in combination with several other anticancer drugs.

Prior to her appointment, Maria had spent a few hours on her laptop looking up different kinds of cancer treatments, including many of the chemotherapy drugs her doctor wanted to prescribe. She found out that methotrexate is commonly used to treat several forms of cancer as well as a few other diseases. She knew that chemotherapy could kill the cancer cells, but all the drugs sounded very powerful, so powerful that she worried they would harm the rest of her body. At her appointment, she asked, “What are these drugs going to do, Dr. Lee? How are they going to kill my cancer without killing me?”

Dr. Lee explained to Maria that methotrexate is an antimetabolite drug, a chemical that blocks normal metabolism in cells. Methotrexate mimics the structure of folate, a precursor or ingredient used to make certain nucleotides. This structural similarity to folate makes methotrexate a substrate analog, an ingredient mimic, for dihydrofolate reductase (DHFR), a key enzyme in the creation of certain nucleotides. Due to their out-of-control growth, cancer cells require more nucleotides than most other normal cells, so methotrexate is particularly toxic to cancer cells.

Maria considered this information and clarified, “But how does the methotrexate tell the difference between the cancer cells and my normal cells, doctor?”

Dr. Lee further explained that the different cells in Maria’s body had different metabolic needs. Most of her cells were not rapidly replicating DNA and dividing so they did not require large pools of nucleotides. “However, a few types of cells do reproduce quickly, such as digestive epithelia and those in the skin that produce hair,” Dr. Lee continued, “so you may experience some side effects such as an upset stomach or hair thinning.” Dr. Lee tried to comfort Maria by explaining that these symptoms were generally mild and should go away once she beat cancer and stopped taking methotrexate.

### Questions

- The chemical structures of folate and methotrexate are shown in Figure 1.
  - Name the chemical groups that differ between the two molecules.
  - Could these differences affect DHFR activity? Why?
- Based on your knowledge of the cell cycle, would you predict that cell cycle arrest would occur sometime in G1, S, G2, or M phase in cells treated with methotrexate?

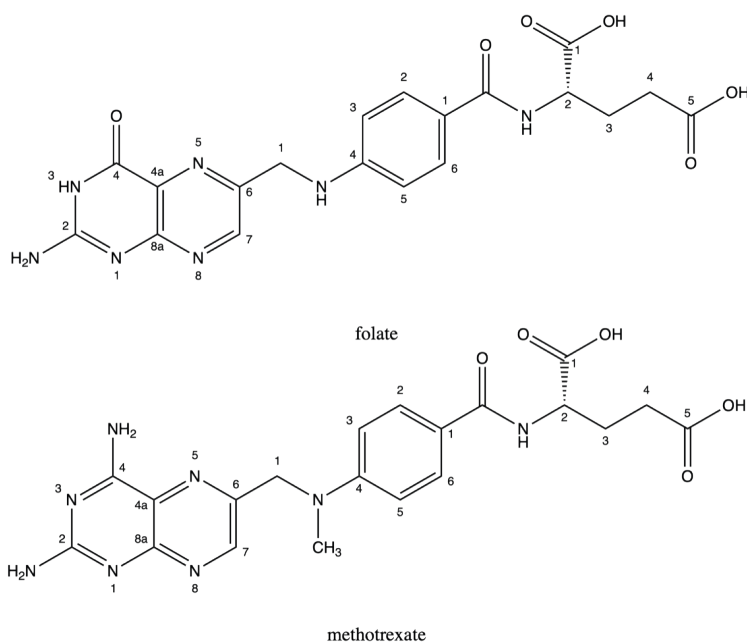


Figure 1. The structures of the normal DHFR substrate, folate, and the competitive inhibitor, methotrexate, are shown. Structures were generated in ChemDraw.

3. A research lab studied the timing of cell cycle arrest in cells treated with methotrexate. They measured the relative amounts of cells able to finish each cell cycle phase. Figure 2 below represents the data they collected. (You can assume that any differences in percentage between 0 hours and 24 hours are significant.) Does this data support or refute the prediction you made in Question 2? Why or why not?

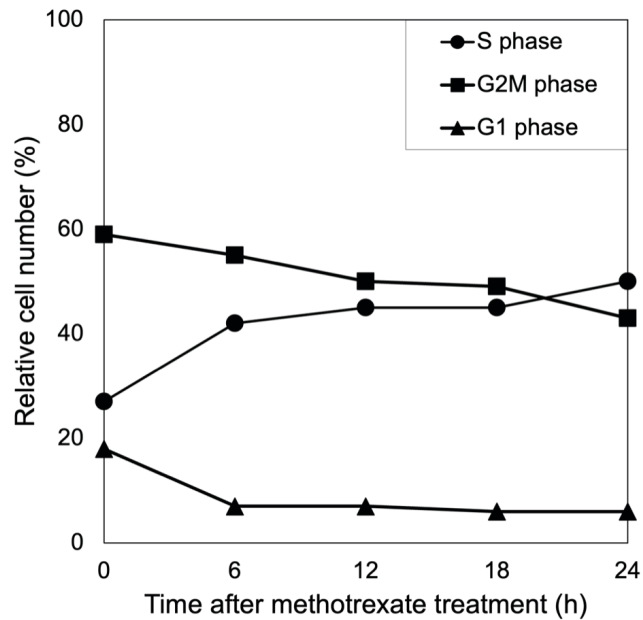


Figure 2. The effect of methotrexate on cell cycle progression. Mock data is plotted based on a similar study by Tsurusawa et al. (1990).

## Part III – Methotrexate History

Maria was intrigued to hear that she was being treated with the first drug used to cure metastatic cancer. After her appointment, she looked up some of the history of the drug and its use in breast cancer treatment. While doing her online research, she learned about Dr. Jane Cooke Wright, one of the pioneering scientists who used methotrexate for cancer treatment and the woman who developed many cancer cell culture techniques still in use today. She watched the following video about Dr. Wright on YouTube:

- *Paying Tribute to ASCO Founder Jane C. Wright, MD.* Running time: 5:22 min. Produced by the American Society of Clinical Oncology (ASCO), 2011. <<https://youtu.be/6hHiWeki9GE>>

### Questions

Use the video that Maria discovered to answer the following questions.

1. How might her unique challenges have prepared Dr. Jane Cooke Wright to tackle problems as big as cancer?
2. How did Dr. Jane Cooke Wright inspire future generations of scientists?



Figure 3. Dr. Jane Cooke Wright. Courtesy of the National Library of Medicine, image from the History of Medicine. <[https://cfmedicine.nlm.nih.gov/gallery/photo\\_336\\_6.html](https://cfmedicine.nlm.nih.gov/gallery/photo_336_6.html)>