

# One Tablet a Day May Keep Cancer Away

by

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Ryan set down his coffee on the receptionist's desk. "Could you check to see who I have scheduled for my 8:30 appointment slot?" Ryan was ready to carry out his pre-appointment review for the first patient of the day.

Dr. Ryan Johnson had come a long way since his initial training as a physician-scientist at the University of California San Diego. The experience of having observed the harsh effects of traditional chemotherapy as a medical resident early in his career guided him to develop a focused interest in cancer biology, medicine, and translational research.

Debra swiveled on her chair. "Your calendar indicates that you will be starting your morning off with Julie Smith," his receptionist replied.

Ryan immediately pictured Julie Smith, a 54-year-old mother of three who had been referred to Ryan 18 months ago after being diagnosed with chronic myelogenous leukemia (CML). CML is a cancerous condition, where myelocytes, a bone marrow derived cell precursor, divide in an uncontrolled fashion, resulting in elevated levels of myelocyte-derived white blood cells (i.e., neutrophils, eosinophils, basophils, and mast cells) in a patient's peripheral blood.

Ryan looked up at Debra. "When she checks in could you send her to the phlebotomist in the clinical laboratory to draw a blood sample? I'll go ahead and place an order for a complete blood count and also initiate a qPCR assay for Philadelphia chromosomal transcript levels."

Ryan briefly reflected on the difficult conversation he had previously had with Julie and her family to explain CML and her disease prognosis. CML stems from a chromosomal translocation, in which part of one arm of chromosomes 9 and 22 swap locations (Figure 1). Two scientists, who first found an association between this specific chromosomal translocation and CML, were working at research institutes in Philadelphia at the time, thus coining the translocated chromosome name. Classically, cytological techniques such as karyotyping and fluorescence in situ hybridization can be used to identify the presence of the Philadelphia chromosome in white blood cells (WBCs), but modern molecular techniques such as reverse transcriptase qPCR can be used for a quick preliminary or follow up analysis.

"Would you like me to start processing her usual Gleevec® prescription?" asked Debra.

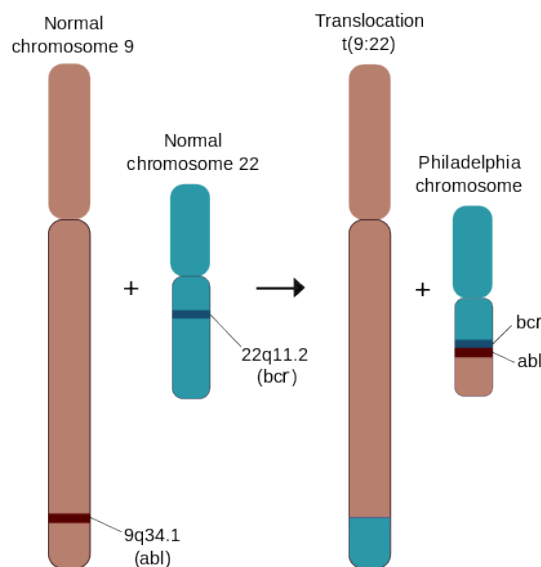


Figure 1. Schematic of the Philadelphia chromosome formation. Credit: Adapted from Aryn89, CC BY-SA 4.0, [https://commons.wikimedia.org/wiki/File:Schematic\\_of\\_the\\_Philadelphia\\_Chromosome.svg](https://commons.wikimedia.org/wiki/File:Schematic_of_the_Philadelphia_Chromosome.svg)

Ryan paused and glanced at Julie's medical charts and pondered the genetic basis for her leukemia. Chromosomal translocations, such as those that create a Philadelphia chromosome, sometimes result in the fusion of two independent genes at the breakpoint of the two translocating chromosomes. In the case of CML, the BCR gene locus on chromosome 22 is fused with the proto-oncogene ABL located on chromosome 9. Testing positive for the presence of the Philadelphia chromosome (Ph<sup>+</sup>) is often part of the clinical diagnosis of CML. The drug Gleevec inhibits activation of the oncogenic BCR-ABL fusion gene product that results from this translocation in CML patients.

Ryan briefly reviewed his notes from Julie's previous appointment. "Let's put a hold on the Gleevec prescription until I analyze the complete blood count results from the lab."

Dr. Johnson had placed Julie on a regiment of the drug Gleevec almost a year and a half ago when she was diagnosed with CML during the accelerated phase of the disease. Julie's symptoms and clinical signs had gone into remission within 15 days after starting the medication. Specifically Julie's WBC count dropped from an elevated ~50,000 per  $\mu\text{l}$  to within a normal range of ~5,000 per  $\mu\text{l}$  and tested Ph<sup>-</sup> (Philadelphia chromosome was undetectable in peripheral blood samples).

Ryan sighed. "Julia may be dealing with Gleevec resistance."

Dr. Johnson was an influential figure in the development of Gleevec and oversaw the clinical trials leading up to FDA approval of the drug. Gleevec, generically known as imatinib, specifically targets a constitutively active version of the ABL tyrosine kinase observed in CML patient white blood cells. The drug competes with ATP for binding to the ATP-binding pocket within the kinase domain specifically with the cancerous BCR-ABL version of ABL tyrosine kinase (CML signaling enzyme), while leaving the normal endogenous protein unaffected (Figure 2).

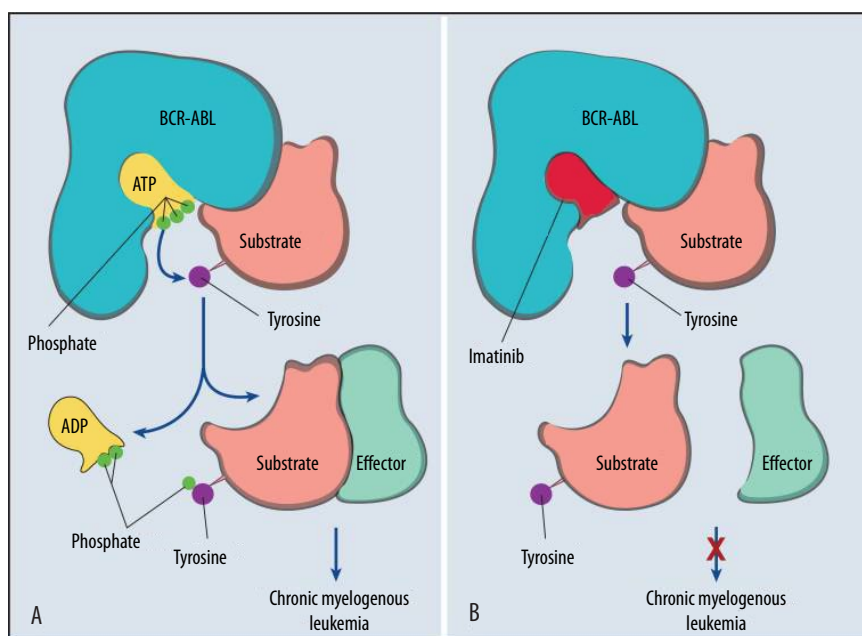


Figure 2. Mechanism of the drug imatinib. Credit: Tamascar and Ramanarayanan (2009).

"Today's clinical tests will help determine if this is the case," said Ryan as he picked up his mug of coffee.

After 18 months of restored health after being diagnosed in the accelerated phase, Julie reported signs and symptoms of CML suggesting a possible relapse of CML. Assuming the clinical results support this scenario, Ryan knew he must come up with an alternative treatment strategy for Julie and explain these options to Julie and her family. Without treatment, patient life expectancy ranges between 4–7 years.

Ryan started to write down his thoughts as he envisioned the canonical tyrosine kinase signaling cascade in his head (Figure 3). He first considered different tyrosine kinase inhibitors as well as other available drugs that have alternative

target proteins in the same signal transduction pathway that is hyper-activated in CML patients. Another option would be to consult Julie on considering a bone marrow transplant, which would wipe out her current population of WBCs and replace them with hematopoietic stem cells from an allogeneic donor (Figure 4). Upon reviewing the signal transduction pathway and considering the Kaplan–Meier survival curve below, Ryan deduced what he thought was the most logical hierarchical treatment plan for Julie.

**Questions**

1. What would you expect the clinical laboratory technicians to look for in Julie’s blood smear while carrying out a complete blood count?
2. What is a karyotype and what type of information can it provide a cytogeneticist?

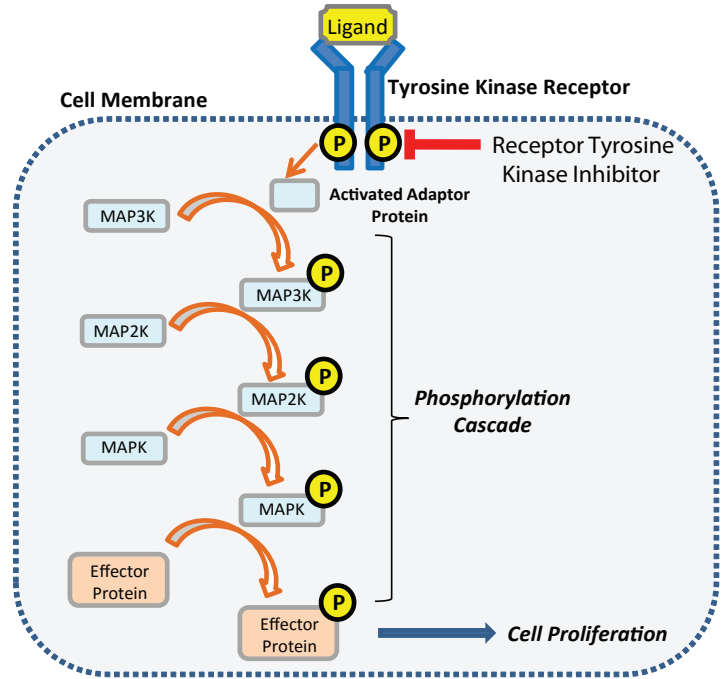


Figure 3. Generic tyrosine kinase signaling cascade. *Credit:* Drawn after Figure 11.10 (phosphorylation cascade) of *Campbell Biology*, 10<sup>th</sup> ed., p. 219.

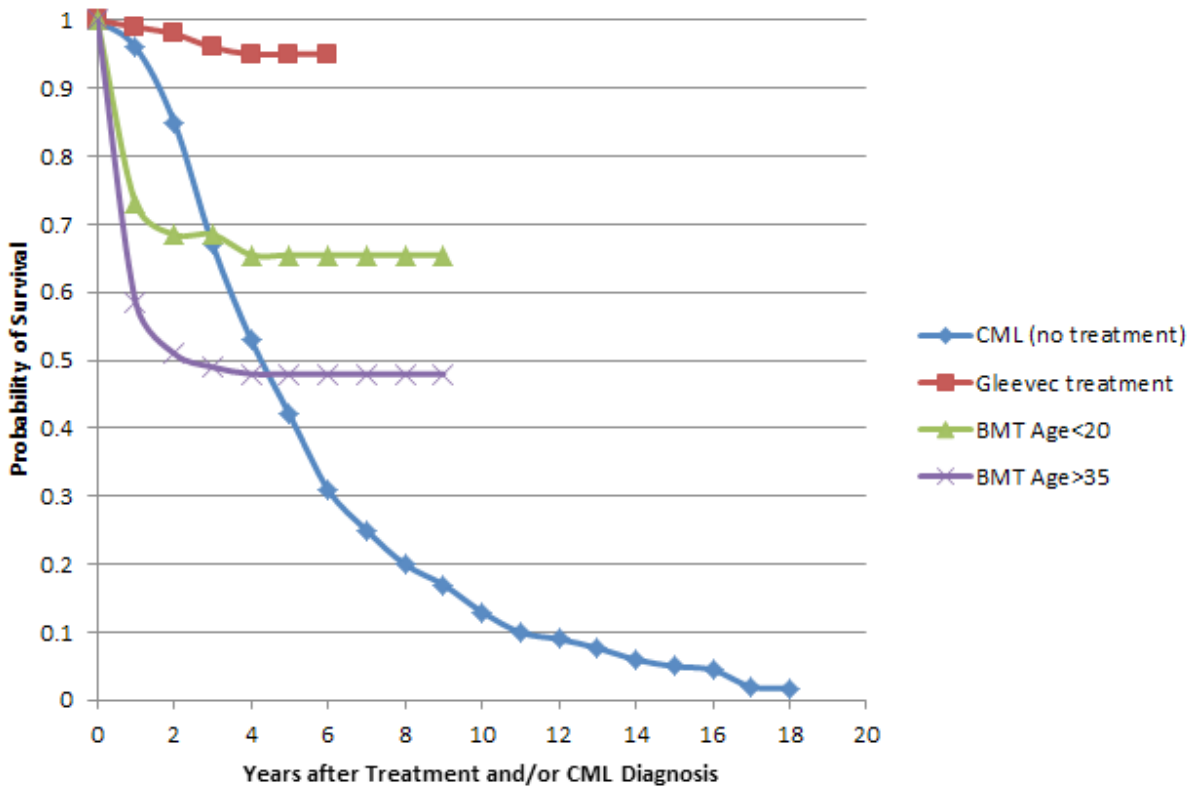


Figure 4. Kaplan–Meier Survival Curve for patients diagnosed with CML  
*Credit:* Based on McGlave et al. (2000), Quintas-Cardama & Cortes (2006), and Lee et al. (1997).

- Describe reverse transcriptase qPCR and relate it to the central dogma of molecular biology.
- Compare and contrast an oncogene with a proto-oncogene.

- Explain the genetic basis of chronic myelogenous leukemia (CML).
- How does Gleevec work at the molecular level?
- Explain a possible scenario at the molecular level that could explain how Julie's CML relapse is independent of Gleevec resistance.
- Assuming Julie's CML relapse is a direct result of Gleevec resistance, outline an explanation on why Gleevec may no longer be effective at the cellular level. Construct a testable hypothesis based on your explanation. Design an experiment to test your hypothesis above addressing why Gleevec is no longer functional against Julie's BCR-ABL.

- Gleevec is used to treat other forms of cancer such as gastrointestinal stromal tumors (GIST) where the drug utilizes the same molecular mechanism of inhibiting aberrant tyrosine kinase signaling. In the case of GIST, Gleevec inhibits the kinase activity of the protein named KIT. Looking at the signal transduction pathway in Figure 5, compare and contrast KIT to the BCR-ABL Gleevec target in Myeloid cells.

- Describe how a pharmaceutical industry scientist could use an enzyme kinetics approach to screen for novel drugs or modified versions of Gleevec that bind more tightly to BCR-ABL or Gleevec resistant forms of BCR-ABL. Describe the appropriate controls for this type of study.

- Outline an optimal treatment plan for Julie and explain your reasoning. Discuss the tradeoffs encountered during the composition of your plan (consider alternative drug targets and a bone marrow transplant).

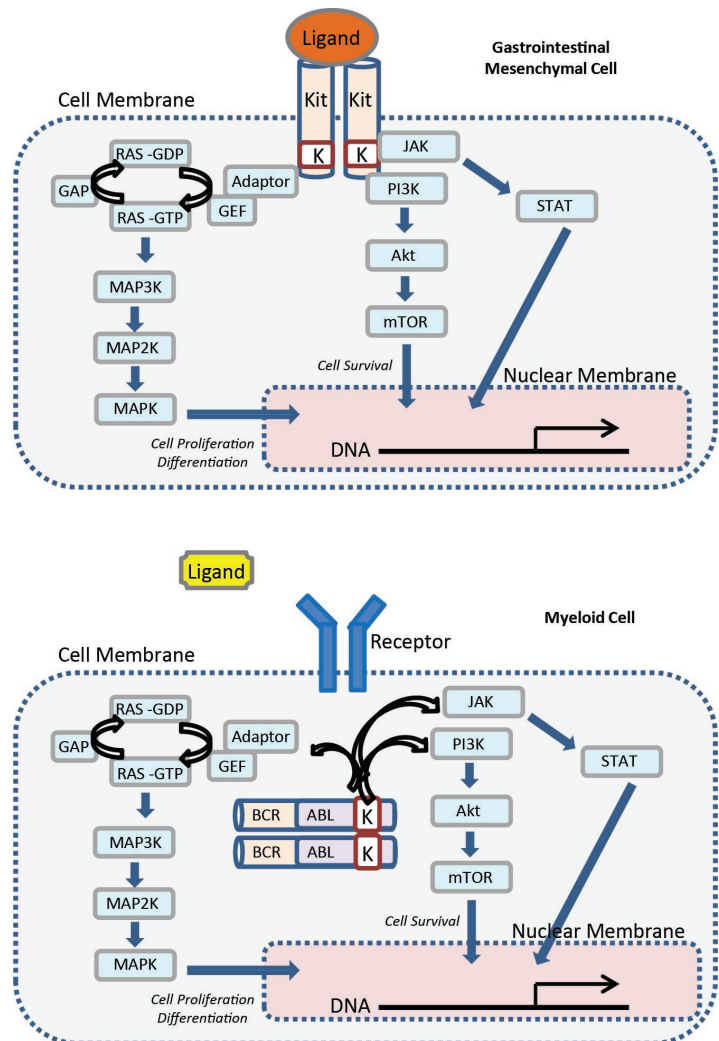


Figure 5. Comparison of tyrosine kinase signal transduction pathways hyperactivated in gastrointestinal stromal tumors (top) and chronic myelogenous leukemia (bottom). Credit: Adapted from Frazer et al. (2007) and Lovly et al. (2014).

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