Gleevec: Rational Drug Design For Cancer
Jonathan Jara-Almonte, David Jensen, Vincent LaRosa, Peter McGrain, and Jessica Sherman
Advisor: Jean Lee
Mentor: Dr. Bob Deschenes, Ph.D., Medical College of Wisconsin

Abstract

Chronic myelogenous leukemia (CML) is a bone marrow cancer resulting from a translocation between chromosomes 22 and 9. This mutation results in the production of C-Abl tyrosine kinase which leads to uncontrolled cell division.

When inactive, the protein is folded into a tight ball. The activation loop is often the site of phosphorylation in the kinase domain. When active, the loop is fully extended in an open position. The remainder of the loop points away from the catalytic center so that the COOH-terminal portion of the activation loop provides an area for substrate binding. This continuously binds with ATP and leads to continuous firing of the chemical messages.

The drug Gleevec is designed to be a competitive inhibitor for the runaway protein. When Gleevec binds with the protein, the NH2 terminal rotates drastically compared to the active conformation. The rest of the loop mimics a substrate binding to the enzyme, thereby blocking the enzyme active site. The protein has shown an ability to mutate into a form that Gleevec no longer inhibits.

Chronic Myelogenous Leukemia

• Characterized by increased and unregulated clonal production of myeloid cells in the bone marrow
• Occurs in 1-2/100,000 people, mostly in the middle age and elderly.
• Symptoms include: malaise, low grade fever, infections, anemia, and thrombocytopenia with easy bruising.
• Occurs in 3 phases: chronic, accelerated, and blast crisis
  • chronic- patients are asymptomatic; duration is variable
  • accelerated- signals that the disease is progressing and the transformation into blast crisis is imminent
  • blast crisis- final phase; rapid progression and short survival

Translocation

The Philadelphia Chromosome

A section of the chromosome on the left (chromosome 9) containing the ABL gene breaks off and switches with a section of the chromosome on the right (chromosome 22) at the BCR region, creating the BCR-ABL fusion gene on chromosome 22.

C-Abl Kinase Structure

• Comprised of mostly beta sheets
• Results from a transcript generated from a gene created from the fusion of the BCR and ABL genes
• When bound with Gleevec, the pyrimidine and pyridine rings of the drug overlap with ATP-binding site and are surrounded by a hydrophobic cage.
• In the following diagram, orange is Gleevec, light blue represents the activation loop, and blue and magenta sections are amino acids binding to the substrate

Gleevec (Imatinib)

• Designed to inhibit the activity of tyrosine kinases (4 specific targets)
• Inhibition prevents substrate binding, inhibiting function, and causes bcr-abl to migrate to nucleus where it’s unable to function
• Mild side effects (edema, nausea, rash, musculoskeletal pain) are common, long term side effects unknown but presumed minimal
• First rationally designed, molecularly targeted therapy for a human malignancy

Escape from Inhibition

• Research has shown that some patients have a form of c-Abl tyrosine kinase that is resistant to Gleevec
• 3 Main Mechanisms of Resistance
  • Decreased intracellular drug levels- glycoprotein binding and efflux from cell
  • Mutations in ABL Kinase of BCR-ABL affecting drug interactions or kinase activity
  • Increased production of tyrosine phosphatase
• 2 Compounds to Replace Gleevec in Development
  • One of which is effective in 14 of 15 known mutations

The above model shows a c-Abl kinase with amino acids known to mutate and cause Gleevec resistance highlighted in blue. Pink regions show predicted possible mutations that could occur in some patients.

References

• www.antigenics.com/diseases/cml.html

Supported by the National Institutes of Health (NIH) – National Center for Research Resources Science Education Partnership Award (NCRR-SEPA)