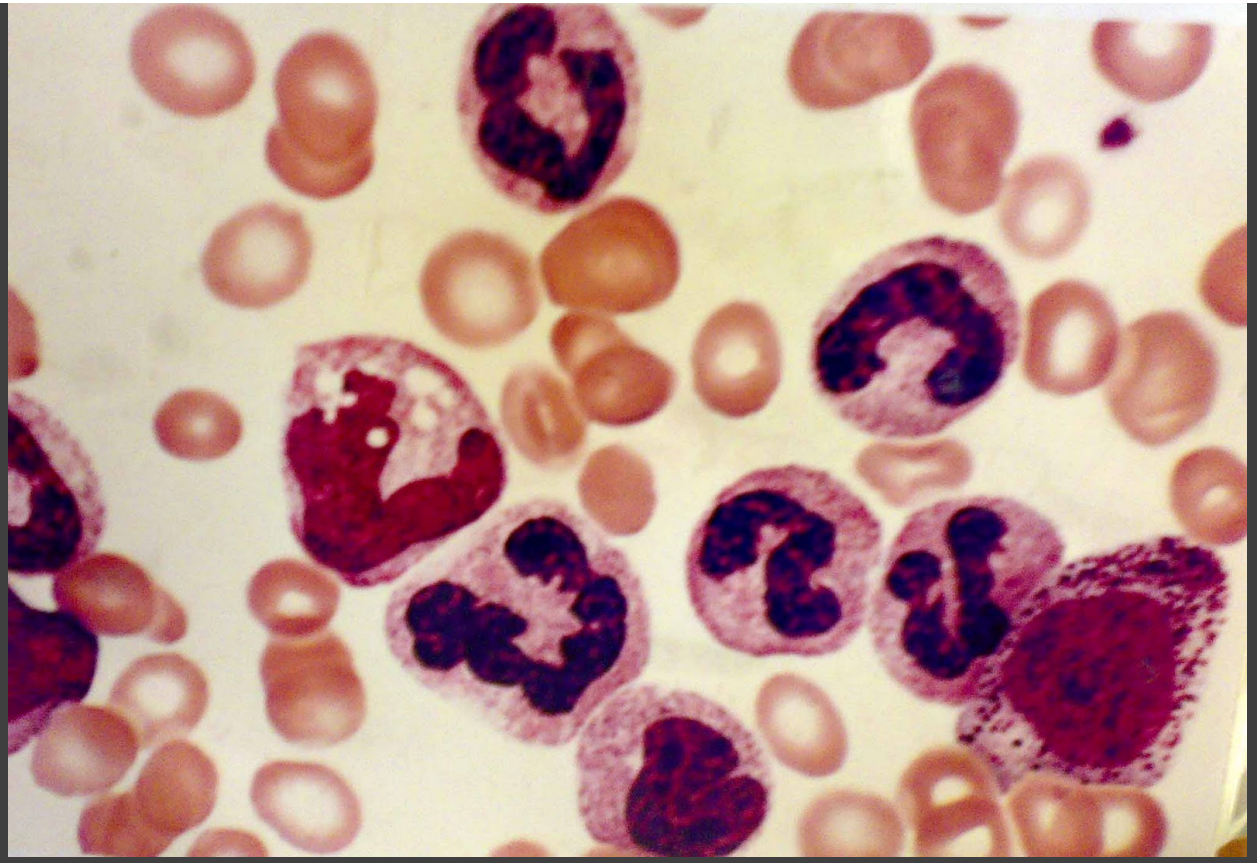


# Chronic Myelogenous Leukemia

*By Ting Huai Shi Pd. 6*

# PHYSIOLOGY

- Chronic myelogenous leukemia (CML) is one of four forms of leukemia.
- It is caused by a spontaneous somatic mutations, and therefore, non-hereditary.
- Unlike most of other leukemia, CML is a late onset disease, manifesting on average at the age of 45-60.
- It causes the stem cells in the bone marrow to produce immature and abnormally functioning myeloid cells, called blast cells, which crowds out and replaces healthy cells.

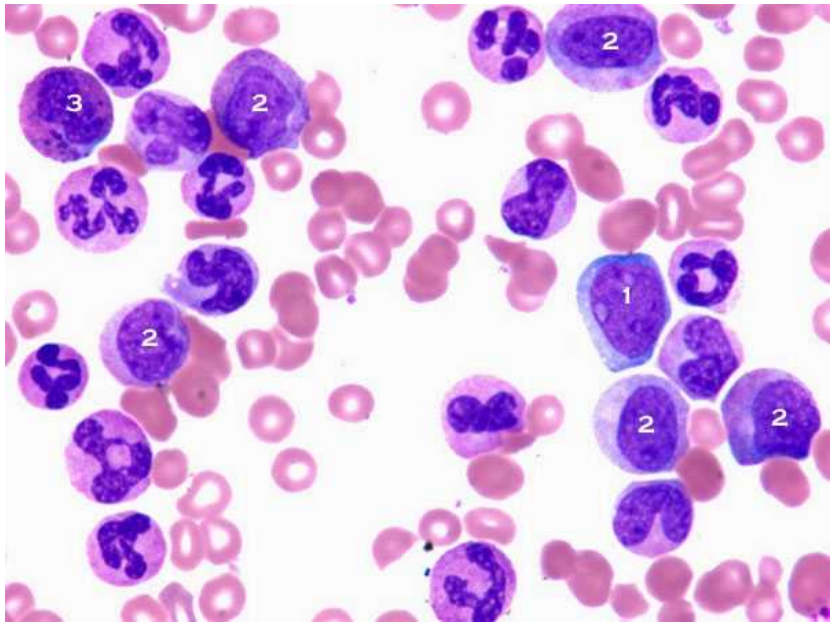



Figure 1

### Phases and Symptoms

- CML develops in three phases. First is the chronic phase, where the patients experience little to no symptoms. These include fatigue, swollen spleen, and joint pains.
- The patients enter the accelerated phase once his blast cell count reaches 10-30%. They start experiencing excessive sweating, and anemia.
- The final, and most dangerous phase is the blast crisis, when the blast cell count reaches more than 30%. In the phase, the disease becomes similar to acute leukemia, and normal treatments stop working. The mortality rate of patients entering the phase is very high.

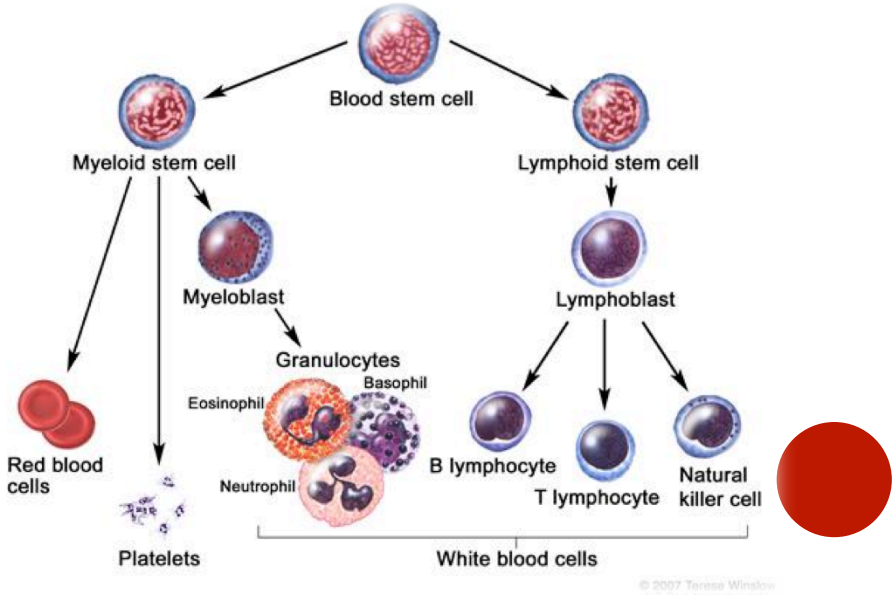



Figure 2

# Molecular Cause

- CML is caused by a chromosomal translocation between chromosomes 9 and 22.
- The BCR gene from 22 fuses with the ABL gene from 9 to form the BCR-ABL oncogene.
- A normal ABL gene codes for a receptor tyrosine kinase (RTK), responsible for the activation of the Ras protein, which acts as a switch for the activation of transcription factors.
- The BCR-ABL oncogene codes a mutated isoprotein of the RTK that is continuously stuck in the activated state, causing unregulated activation of transcription factors.
- The increase in the number of activated transcription factors lead to uncontrolled stem cell differentiation, slowly producing large numbers of blast cells.

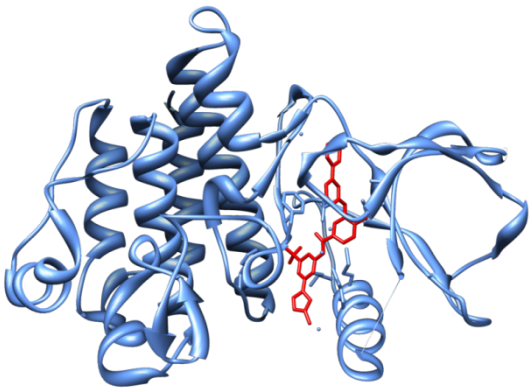


Figure 3

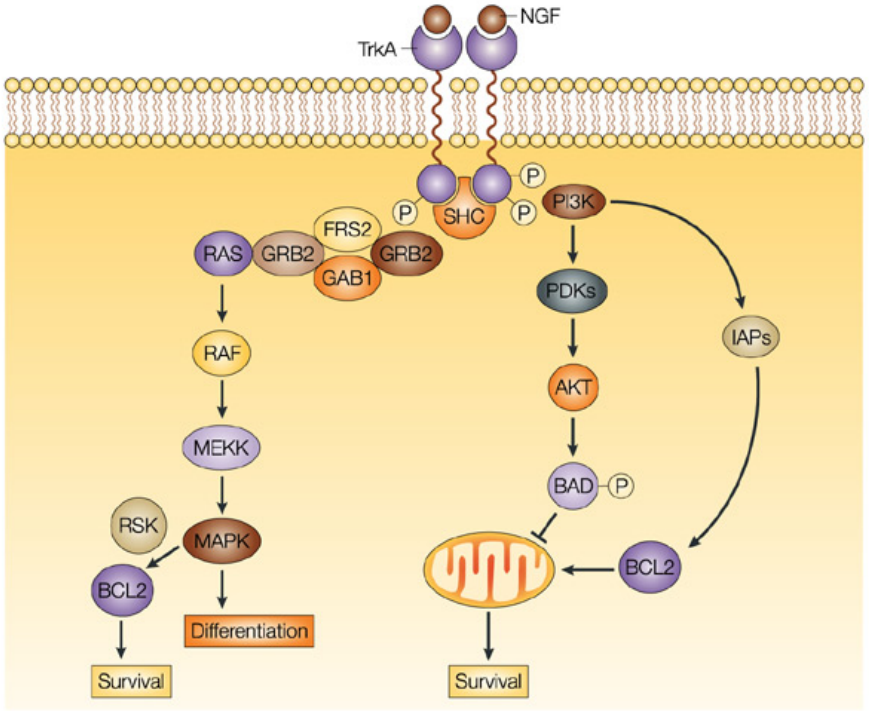



Figure 4

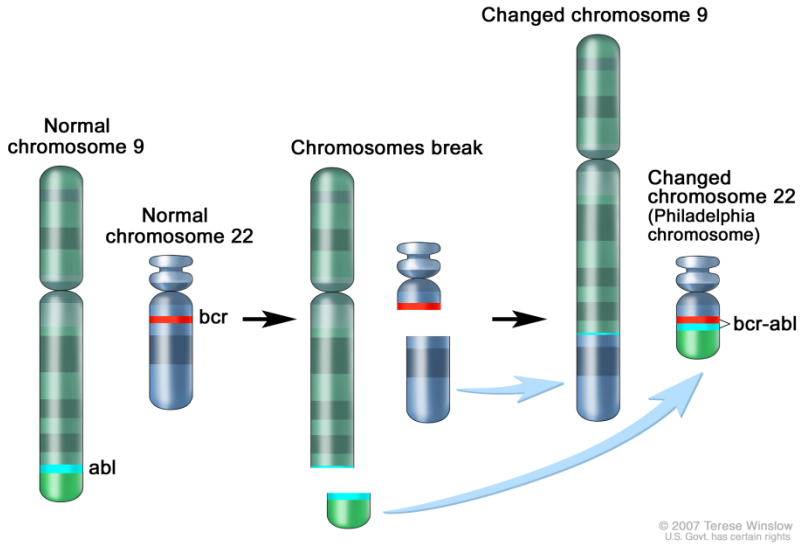
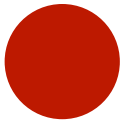



Figure 5

# Current Treatments and Therapies

- The most common treatment for CML is the use of tyrosine kinase inhibitors (TKIs), such as inmatinib (Gleevec), or nilotinib.
- TKIs inhibit the function of RTKs, stopping it activation, and the activation of further transcription factors. This causes the cancerous stem cells to stop differentiating, and eventually die out.
- While this stops the production of further blast cells, it will not eliminate already existing blast cells, making it most effective in the chronic or early accelerated phase, when blast cells counts are still low. TKIs are a very effective treatment, able to eliminate all symptoms of CML it continuously taken.
- The remaining blast cells will slowly die out, causing the patient to go into remission. However, most of the time the disease will relapse, even year after, if TKIs aren't continuously taken.
- If the disease has progress to the point where TKI are no longer as effective, more extreme treatment must be used. Chemotherapy is also commonly used to treat CML patients.
- The most common drug used is hydroxycarbamide, a type of antimetabolite, which interferes with DNA replication in cells, causing cells that divide to die. It targets cells that divide often, such as cancer cells, but also healthy body cells such as hair follicles, skin cells, and normal blood cells. This is why chemotherapy comes with many side effects, such as such as hair loss, nausea, fatigue, and anemia.
- For even more severe cases, such as those patients in late blast crisis, the only cure is a bone marrow transplant. This procedure is very dangerous, and comes at a high rate of failure. It is only used as a last resort to save a patient's life. Success rate depend on the situation the patient is in, and how well the tissue type of the donor matches, and it can range from 20-30% in worse scenarios, to 70-80%.

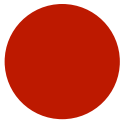


# Proposed Cure and Limitations

- Immunotherapy has been tested on numerous other types of cancer, and has given good results. However, it has never been used for CML before.
- Immunotherapy takes advantage of the immune system's natural ability to fight cancer, and amplify it to fully combat it.
- The killer T-cells, or cytotoxic T-lymphocytes (CTL) are able to produce receptor to foreign antigen, and kill the targeted cell. It is able to do this with cancer cells as well, but due to their similarity with normal body cells, CTLs sometimes let a few slip past detection. Those few are the ones that proliferate can causes cancer.
- Each cancer cell have their own specific antigen, called tumor specific antigens (TSAs) that CTLs can recognize. CTLs can be genetically engineered to express receptors to specific TSAs, allowing them to target and kill the cancer cells.
- For CML, the most effect TSA would be the oncogenic RTK codes by the BCR-ABL oncogene. First, the CTLs are filtered out of the patient's blood through apheresis, which separates blood constituents by centrifugation. The CTLs are then inserted with a gene that codes for a receptor to the oncogenic RTK, allowing them to target and kill cancerous blast cells and stem cells that carry this TSA.

**Problems and Limitations**

- In most cases, the CTLs will not be able to wipe out all of the cancerous cells, causing the patient to go into remission, only to have it relapse later on. In this time, the disease could have progressed into more serious phases without the patient realizing.
- For cases where the patient is experience late phase CML, this treatment would be less effective, due to less available CTLs to manipulate and more cancer cells to combat. However, this can be solved by accepting blood donations from people with similar blood types.
- The inserted gene must code for a receptor to only the mutant RTK, not the normal one, since that would cause the CTLs to attack healthy cells, causing an autoimmune crisis.



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**Images**


- Figure 1: http://www.pathpedia.com/education/eatlas/imagepedia/chronic_myelogenous_leukemia_(cml),_blood.aspx
- Figure 2: http://www.cancer.gov/images/cdr/live/CDR526538-571.jpg
- Figure 3: http://upload.wikimedia.org/wikipedia/commons/thumb/a/a3/3CS9_Abl1_Nilotinib.png/800px-3CS9_Abl1_Nilotinib.png
- Figure 4: http://www.nature.com/nrc/journal/v3/n3/images/nrc1014-f4.jpg
- Figure 5: http://www.stfranciscare.org/saintfrancisdoctors/cancercenter/nci/media/CDR0000533336.jpg