CASE COMPREHENSIVE CANCER CENTER

Chronic Myelogenous Leukemia

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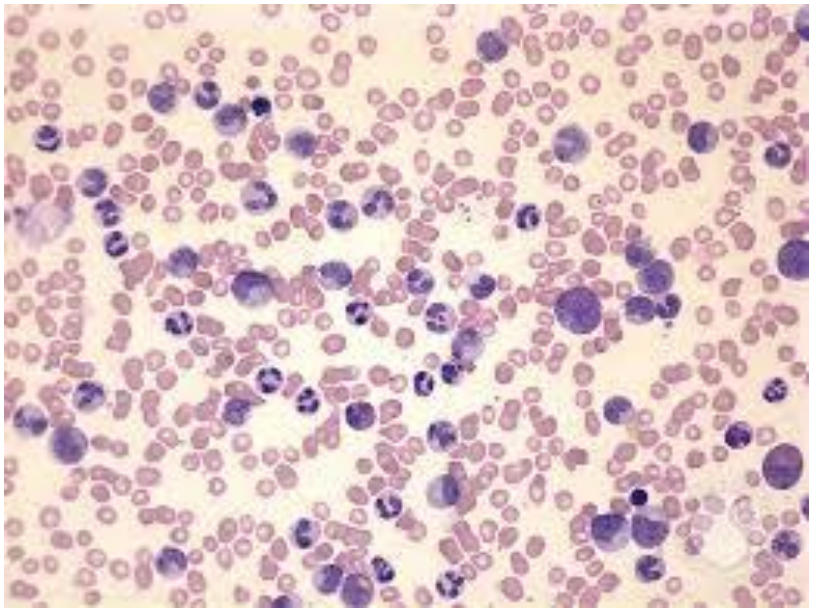
Outline of CML Talk

- Brief Description of Pathophysiology of Chronic Myelogenous Leukemia (CML)
- Brief History of Medical Discovery in CML
- Current Treatment Options for CML
- Side Effect Management
- CML Disease Monitoring
- Future Directions in the Treatment of CML
- Discussion of Cost Issues Associated with the Treatment of CML
- CML Cases
- Question and Answer Period

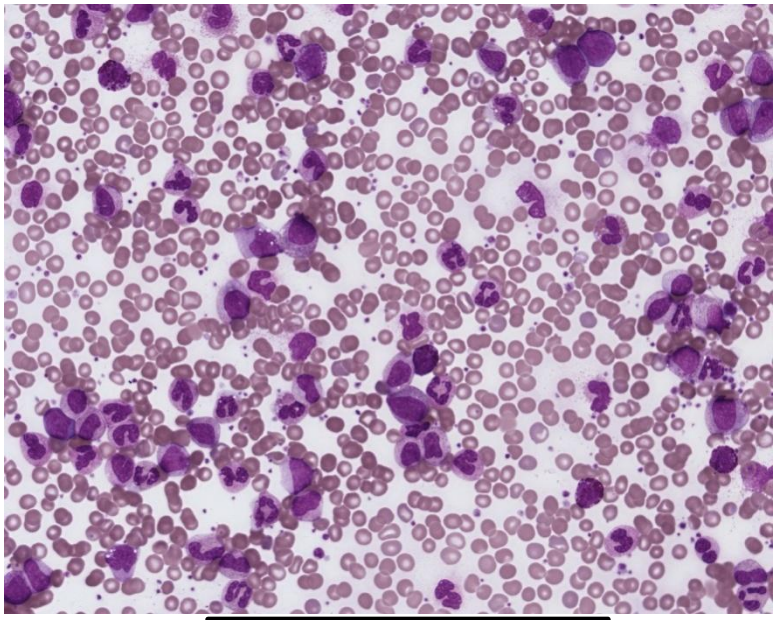
Chronic Myelogenous Leukemia

- Slow growing cancer of the Granulocytes (type of white blood cell) – a type of Myeloproliferative Neoplasm (MPN)
- Approx 6600 new cases per year in United States (2014)
- Approx 1100 deaths per year in United States (2014)
- Median Age at diagnosis 67 years old (rarely found in children)

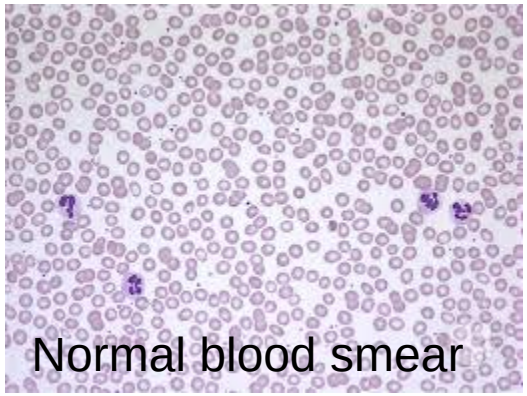
CML Blood Smear



CML Blood Smear



CML Blast Crisis



Normal blood smear

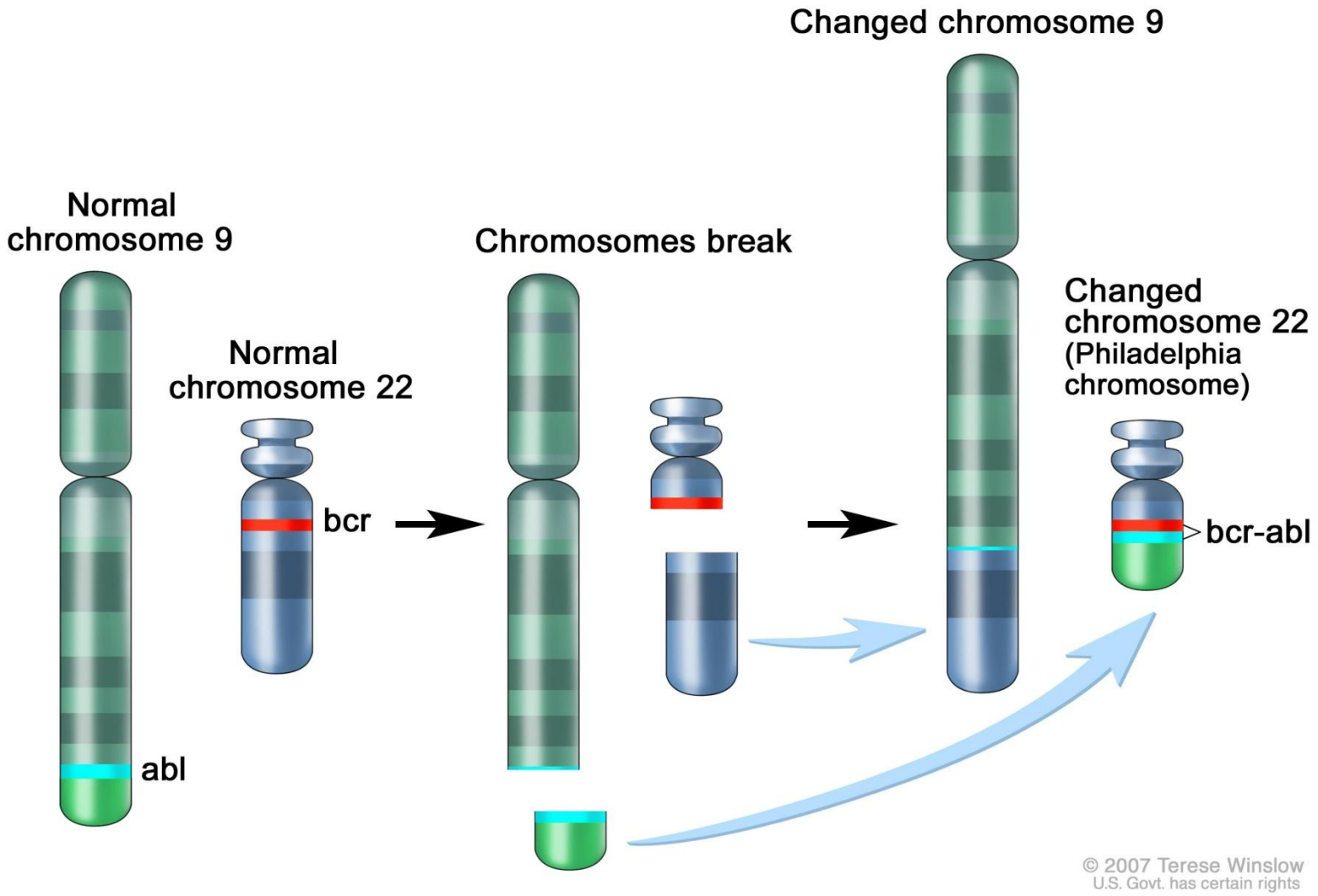
Chronic Myelogenous Leukemia

- Possible Symptoms of CML:
  - Night Sweats
  - Enlarged Spleen (Abdominal swelling in the Left Upper Quadrant sometimes with tenderness)
  - Fatigue and/or weakness
  - Bone pains
  - Fevers
  - Frequent Infections
  - Early Satiety and/or Weight loss

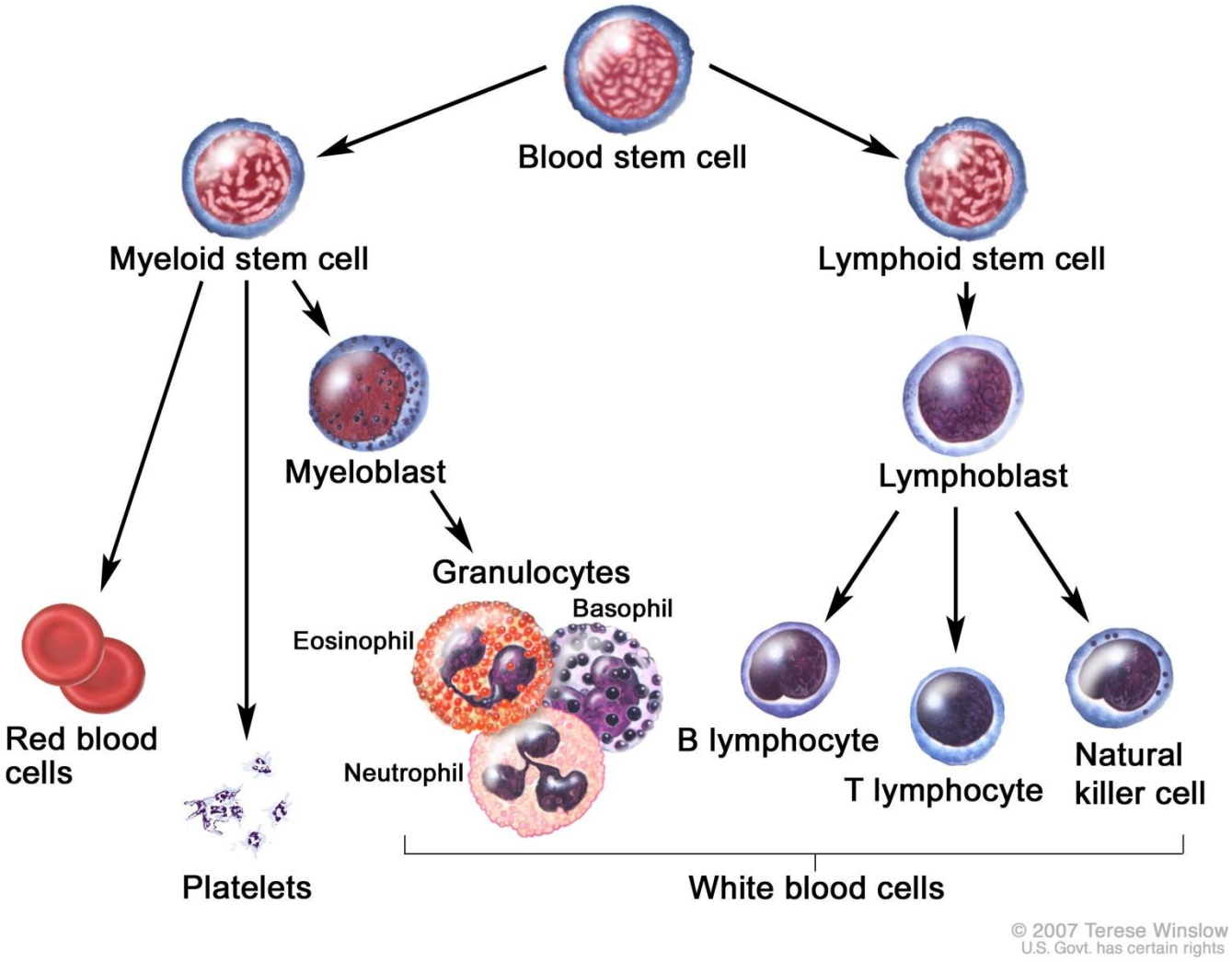
Chronic Myelogenous Leukemia

- A single chromosomal translocation may be responsible for the disease (very unusual)
- Translocation of long arm of chromosome 9 and long arm of chromosome 22
- The resultant BCR/ABL gene yields an abnormal protein
- The BCR/ABL encoded protein is permanently “on” leading to inappropriate cell division from hematopoietic stem cells to cancerous granulocytes in the bone marrow

9;22 translocation, BCR-ABL fusion



Hematopoietic Stem Cell Differentiation



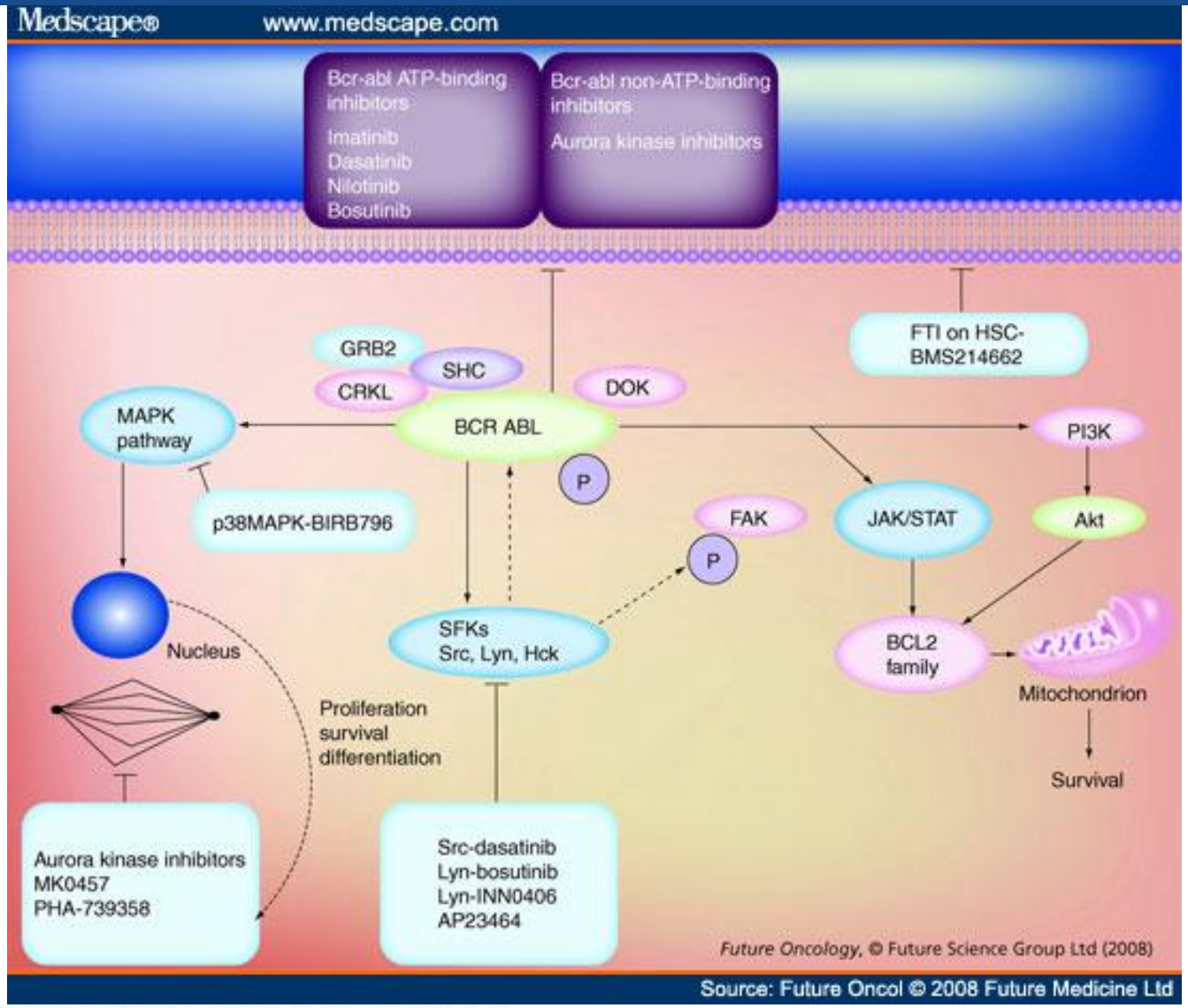
What is the BCR gene?

- BCR (Breakpoint Cluster Region) gene encodes a protein that may be a serine/threonine kinase but is of unknown function.
- The amino-terminus of the BCR protein may confer extra stability and therefore extra long life to BCR/ABL fusion protein.

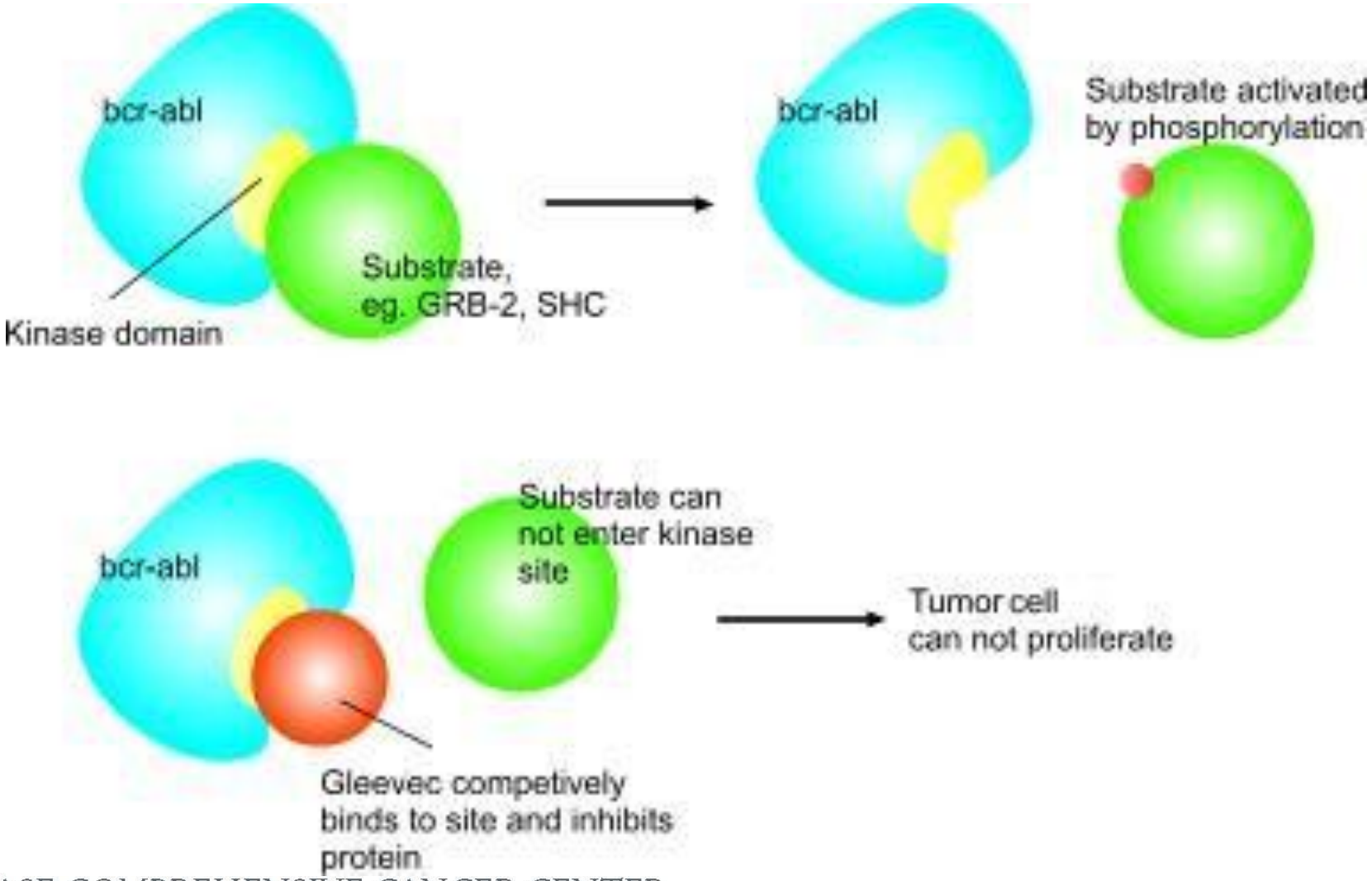
What is the ABL gene?

- **ABL (Abelson)** is an oncogene (a gene that when over-expressed causes cancer) originally identified in a leukemia virus
- **ABL - tyrosine kinase protein**
  - **Involved in the signalling pathway leading to the production of granulocytes from hematopoietic stem cells**
- **The BCR/ABL tyrosine kinase protein is the target for most directed therapies in CML treatment**

ABL function



Inhibition of ABL kinase by Gleevec



Stages of CML

- **Chronic Phase**
  - <10% blasts (acute leukemia cancer cells)
- **Accelerated Phase**
  - 10-29% blasts and/or resistance to primary therapy
- **Blast Crisis (a type of acute leukemia)**
  - > 30% blasts
- **Sokal Risk Score** (high, intermediate or low risk)
  - Age, spleen size, blast #, platelet count
- **Hasford Risk Score** (high, intermediate or low risk)
  - Age, spleen size, platelet count, blast #, basophil #, eosinophil #

Brief History of CML

- **Peter Nowell MD**
  - **1961**: Discovered Philadelphia (Ph1) Chromosome abnormality in almost all patients with CML
- **Janet Rowley MD (Human geneticist)**
  - **1973**: Discovered that the Ph1 Chromosome was a translocation of chromosome 9 & chromosome 22
- **David Baltimore PhD (Molecular biologist)**
  - **1990:** Showed that mice expressing BCR/ABL developed CML

Brief History of CML (continued)

- **Brian Druker MD**
  - **1996**: Demonstrated Imatinib (Gleevec) – an ABL tyrosine kinase inhibitor stopped CML cell growth in the petrie dish.
  - **2001:** Demonstrated safety and efficacy of Imatinib in patients with CML
- **2001: FDA Approval of Gleevec for CML**

Treatments for Chronic Phase CML

- **Tyrosine Kinase Inhibitors** (year of FDA approval)
  - **Imatinib (Gleevec) 2001**
  - **Dasatinib (Sprycel) 2006**
  - **Nilotinib (Tasigna) 2007**
  - **Bosutinib (Bosulif) 2012**
  - **Ponatinib (Iclusig) 2012**
- **Protein Translation Inhibitor**
  - **Omacetaxine (Synribo) 2012**
- **Interferon alpha**
- **Hydroxyurea**
- **Allogeneic Stem Cell Transplant**

Treatment for Acute Phase CML

- **Tyrosine Kinase Inhibitors**
- **Hydroxyurea**
- **High dose Cytarabine**
- **Busulfan**
- **Interferon alpha**
- **Omacetaxine**
- **Allogeneic Stem Cell Transplant**
- **Clinical Trial when available**

Treatment for Blast Crisis CML

- **Tyrosine Kinase Inhibitor**
- **Acute Leukemia Induction Chemotherapy**
- **Allogeneic Stem Cell Transplant**
- **Clinical Trial when available**

Imatinib (Gleevec)

- Must take one 400 mg tablet daily lifelong (not a cure)
- High cost (400 mg tablets of Gleevec cost $6980 for just 30 tablets)
- Imatinib going generic soon?
- Relatively few side effects
- High efficacy
  - 89% of patients alive at 7 years after initiation of imatinib compared to 68% of patients alive at 5 years prior to the FDA approval of imatinib

Side Effects of Imatinib and Management of Side Effects

- **Drop in blood counts**
  - Adjust dose
- **Elevation in liver enzymes**
  - Adjust dose
- **Fluid retention/peri-orbital edema**
  - Diuretics, heart echo, adjust dose, surgery
- **Nausea**
  - Take with meals and large glass of water, anti-nausea meds
- **Muscle cramps**
  - Calcium supplementation, tonic water
- **Rash**
  - Topical or systemic steroids, adjust dose
- **Diarrhea –** anti-diarrhea meds, adjust dose

Dasatinib (Sprycel)

- One 100 mg Tab dose daily
- Expensive (30 tabs cost $10,572)
- May be more efficacious than Imatinib
- No survival benefit over Imatinib
- More side effects, more interactions with other medications than Imatinib

Side Effect Management in Dasatanib

- **Drop in Blood Counts**
  - Adjust dose
- **Pulmonary Arterial Hypertension**
  - Stop Dasatanib
- **Pleural & Pericardial Effusions, Fluid Retention**
  - Diuretics, steroids, dose reduction
- **Fluid Retention**
  - Diuretics
- **Nausea**
  - Take with meal and large glass of H2O, anti-emetics
- **Rash** – topical or systemic steroids, adjust dose.

Nilotinib (Tasigna)

- One 300 mg tablet twice a day
- Expensive (approx $10,000 per month)
- Possible cardiac toxicity and Arterial blood clots
- May be more efficacious than Imatinib
- No demonstrated survival advantage over Imatinib
- More side effects and medication interactions than Imatinib

Management of Nilotinib Side Effects

- **Blood Count Drops**
  - Adjust dose
- **QTc prolongation** (can cause fatal heart arrhythmias)
  - Adjust dose or stop, check potassium and magnesium
- **Elevated liver and/or pancreatic enzymes**
  - Adjust dose or stop
- **Blood sugar changes**
  - Treat with anti-hyperglycemic meds
- **Peripheral Arterial Occlusive Disease**
  - Stop Medicine – consider alternative therapies in patients with h/o PAOD and CAD
- **Rash –** topical or systemic steroids.

Bosutinib (Bosulif)

- Treatment for CML resistant to other TKI's or patient intolerance to other TKI's
- One 500 mg tablet daily
- Expensive (approx $8000 per month)
- More side effects than Imatinib

Management of Bosutinib Side Effects

- **Drop in Blood Counts**
  - Adjust dose
- **Elevated Liver Enzymes**
  - Adjust dose, stop med
- **Diarrhea**
  - Anti-diarrhea meds, adjust dose, stop med
- **Fluid Retention**
  - diuretics
- **Nausea**
  - Take with a meal and/or large glass of H2O, anti-emetics
- **Rash –**Topical or systemic steroids, adjust dose

Ponatinib (Iclusig)

- **Withdrawn** from market for a period of time due to **Vascular Occlusion** in 27% of patients.
- One **45 mg tablet** once daily
- Indicated for **CML resistance** with **T315I** mutation or failure/intolerance of all other TKI's
- **Expensive** ($9850 per month)
- **Lots of Potential Side Effects**

Ponatinib Side Effect Management

- **Signs of heart attacks, strokes, DVT**
  - stop med, treat event
- **Drop in Blood Counts**
  - Adjust dose, growth factors
- **Liver and pancreatic dysfunction**
  - Adjust dose or stop med
- **Bleeding**
  - Stop med, treat hemorrhage
- **Cardiac Arrhythmias**
  - Stop med, treat arrhythmia
- **Fluid Retention –** diuretics, dose interruption/reduction/cessation
- **Hypertension -** Medically treat hypertension
- **Rash –** Topical or systemic steroids, dose adjustment/cessation

Omacetaxine (Synribo)

- Given only to Pt's with **Intolerance to or Progression on TKI's**
- **Subcutaneous injection twice daily** 14 days on 14 days off until hematologic response and then maintenance injections twice daily 7 days on and 21 days off.
- **Not a cure**
- **Less efficacious than TKI's**
- **Few side effects**

Monitoring for Response with Therapy

- **Blood Counts** (CBC's)
- **Spleen measurements**
- **FISH** for peripheral blood **9;22** translocation
- **PCR** for peripheral blood **bcr/abl** transcript
- **Bone Marrow Biopsy**
- **Mutational Analysis** of **bcr/abl** transcript if inadequate response or if relapse or progression of disease

Timing of Follow Up Tests for Chronic Phase CML

- Bone Marrow Biopsy at Diagnosis
- FISH for 9;22 to confirm diagnosis
- Quantitative PCR of bcr/abl at diagnosis and every 3 months for 2 years after no evidence of detectable transcript.
- Mutational Analysis of bcr/abl transcript if 1 log increase in bcr/abl transcript or relapse from undetectable to detectable transcript or progression into accelerated phase or blast crisis.

Treatments for CML on the Horizon

- **Farnesyl Transferase Inhibitors**
  - Lonafarnib and Tipifarnib
- **T315I mutation agents**
- **Histone Deacetylase Inhibitors**
  - Panobinostat
- **Proteosome Inhibitors**
  - Bortezomib

TKI Cessation in “Cured” CML patients?

- Clinical trials of TKI cessation are ongoing
- Preliminary data suggest that a subgroup (approx 40%) of PCR - BCR/ABL negative patients can stay in remission for a prolonged period of time.
- Studies ongoing to pre-identify those patients who:
  - Stay in remission after TKI cessation
  - Whether these patients are truly “cured”

Cost Issues and CML Treatment

- **High monthly cost of life-long treatment**
  - **$6,000 to $14,000** per month lifelong cost to healthcare system
- **Patient Position**
  - Affordable
  - Effective Therapy
  - Minimal Side Effects

Pharmaceutical Company Position

- **Patients and doctors requesting new medications**
- **High cost of drug development (approximately $1 billion dollars to develop 1 new cancer therapy medication)**
- **Rare diseases need financial incentive to develop new drugs**
- **Most new medications developed in United States**
- **High costs balanced by generous patient assistance programs**

Health Care/Insurance System Position

- Increasing Costs of Lifelong Medications May Bankrupt System
- No legal ability to regulate or negotiate medication costs
- Increasing costs of meds increase cost of insurance premiums

Physician Position

- **Balance**
  - New medications need to be developed by pharmaceutical companies
  - No bankruptcy of health care system
  - Medications readily available to patients
  - Medications affordable to patients that need them

Physician and Consumer Questions

- **Why did cost of Gleevec rise?**
  - **$2200** per month in **2001**
  - **$7000** per month in **2015**
  - **$14** per month to manufacture (Andrew Hill – Univ of Liverpool)
  - Theoretically recouped development investment by end of **2004**
- **Why is Imatinib not yet available as a generic?**
  - Newest release date of generic Imatinib July 2016
  - Imatinib (the chemical structure) initially due to be off patent January 2013
  - Final patent expiration of beta crystal of Imatinib 2019

Case #1: 34 yo male with symptoms of weight loss and abdominal discomfort

- CBC: WBC 250,000, hemoglobin 9.5, platelet 104,000, enlarged spleen on physical exam.
- FISH positive for BCR/ABL
- Bone marrow biopsy showed chronic phase CML, BCR/ABL PCR showed 73% transcripts
- Hydrea started until wbc < 70,000 and then Imatinib (Gleevec) 400 mg daily
- After 3 months wbc 4.5, hemoglobin 14.5, platelets 165,000, BCR/ABL PCR 9% transcripts
- After 6 months normal CBC, BCR/ABL PCR – undetectable
- 7 years later, undetectable BCR/ABL. Side effects of muscle cramping from Gleevec.

Case #2: 76 yo female with abdominal discomfort and night sweats

- CBC with diff showed wbc 135,000, hemoglobin 12, platelets 104,000, elevated neutrophils and basophils
- Physical Exam showed splenomegaly with spleen 5 cm below left rib cage
- BCR/ABL FISH was positive
- Bone marrow aspirate and biopsy consistent with chronic phase chronic myelogenous leukemia.
- BCR/ABL PCR showed 78% transcripts.
- Hydroxyurea started and then switched to Imatinib (Gleevec) 400 mg daily once wbc < 70,000.
- After 3 months of Gleevec, WBC 35,000, hemoglobin 9.5, platelets 70,000 and BCR/ABL PCR 53%

Case #2 continued

- Gleevec stopped
- CBC recovered to wbc 50,000, hemoglobin 10.5, platelet 115,000
- Dasatanib (Sprycel) 100 mg started
- Patient developed side effects of fluid retention, nausea, diarrhea, and rash
- CBC after 1 month showed wbc 500, hemoglobin 7.9, platelets 15,000, BCR/ABL PCR 35% and Sprycel stopped
- After 3 months CBC recovered to WBC 17,000, hemoglobin 10.2, platelets 105,000

Case #2 continued

- Nilotinib (Tasigna) started at 300 mg twice daily
- After one month CBC showed WBC 2,500, hemoglobin 9.5 and platelets 35,000 and nilotinib stopped. Pt otherwise without symptoms, splenomegaly resolved.
- After 6 weeks CBC recovered to WBC 11,000, hemoglobin 10.9, platelets 115,000.
- Nilotinib restarted at 200 mg twice daily
- After 3 months WBC 4,900, hemoglobin 12.0, platelets 85,000, BCR/ABL PCR 15%
- After 2 years on Nilotinib 200 mg twice daily BCR/ABL PCR 1%

Case #3: 61 year male presented with malaise and fatigue

- CBC showed wbc 96,000, hb 11, plt 114,000
- Started on Gleevec 400 mg daily
- Pt on and off Gleevec for 7 years with BCR/ABL transcript level rising or falling
- Always had detectable BCR/ABL transcript
- Off Gleevec and lost to follow up for over 1 year until patient hospitalized for fever and weight loss.
- CBC showed wbc 140,000 with 25% blasts

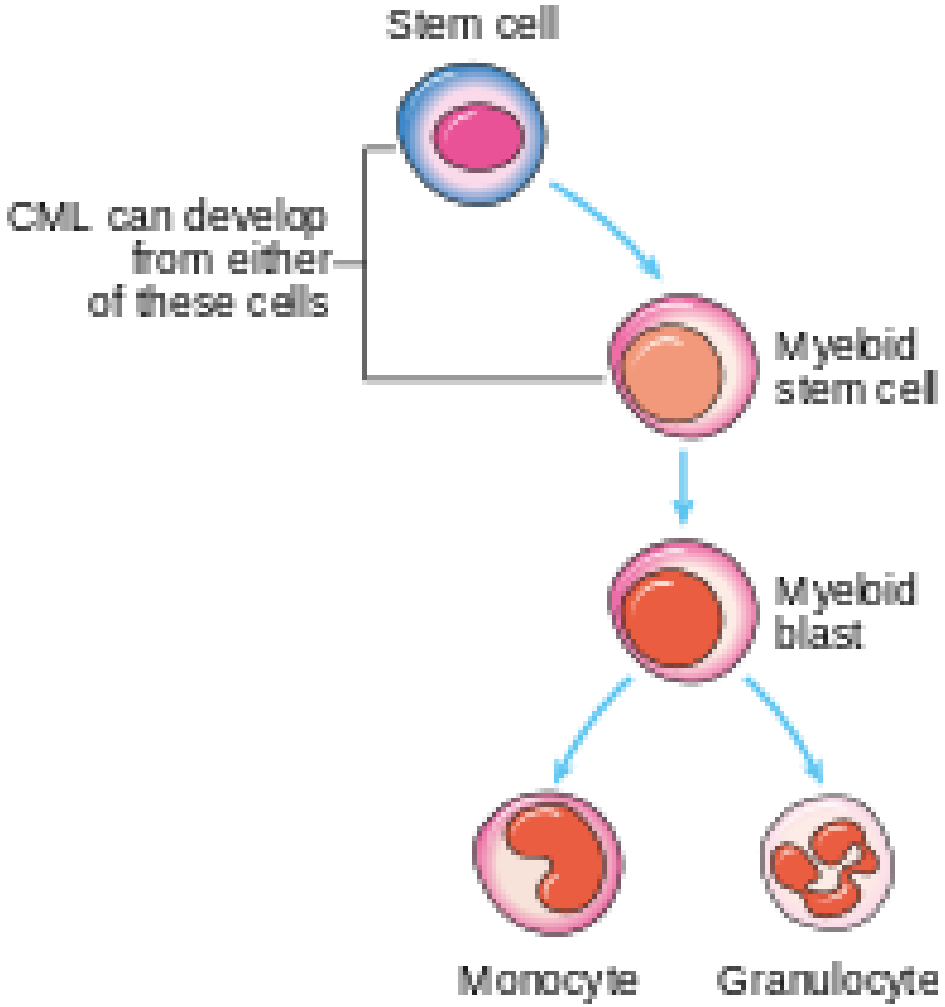
Case #3 continued

- Started on Dasatinib and given acute leukemia chemotherapy (Daunarubicin and Cytarabine)
- Allogeneic transplant after patient in remission
- Recovering slowly from transplant with significant graft versus host disease

Case #4: Healthy 44 year old with elevated WBC at PCP office

- CBC showed 53,000 wbc, elevated eosinophils, neutrophils and basophils.
- Bone marrow biopsy showed chronic phase CML, FISH positive for 9;22 translocation and PCR for BCR/ABL was 43%
- Gleevec started and normal wbc, undetectable BCR/ABL transcript.
- Side effects of fluid retention and peri-orbital edema.
- Diuretics started, plastic surgery on eyelids
- Symptom-free in continued remission x 7 years

Questions?


Stem cell
CML can develop from either of these cells
Myeloid stem cell
Myeloid blast
Monocyte
Granulocyte