FOCUS ON LEUKEMIA, LYMPHOMA and MYELOMA:

HODGKIN LYMPHOMA

T-CELL LYMPHOMAS

RADIATION THERAPY FOR LYMPHOMA

Jakub Svoboda, MD
John Plastaras, MD, PhD
University of Pennsylvania
November 6, 2009

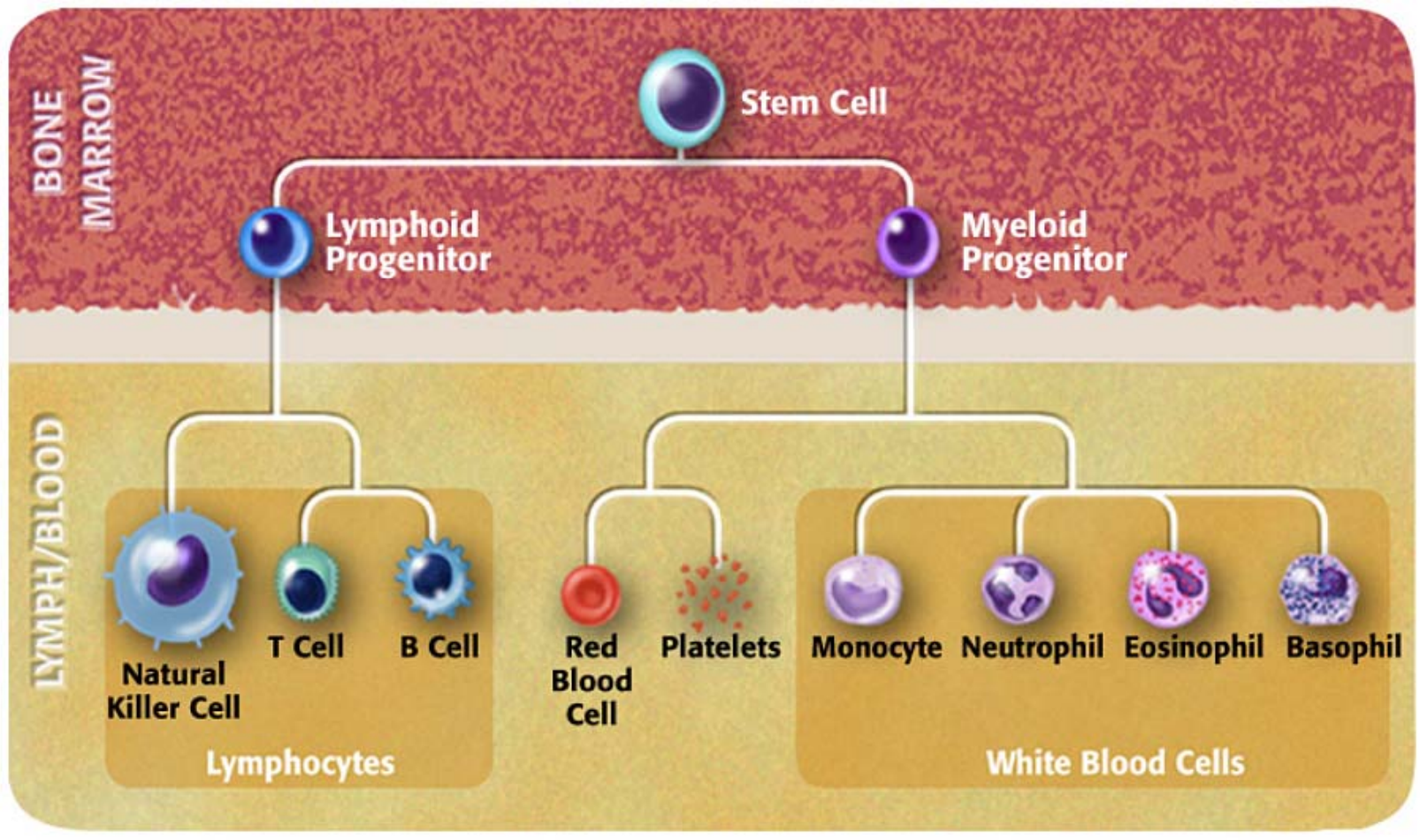
Outline

- Terminology
- Lymphoma
  - Diagnosis and staging
  - Principles of therapy
  - Research areas
- Hodgkin Lymphoma and T-cell Lymphoma
  - Standard treatments
  - Relapsed/Refractory disease
  - Novel therapies
- Radiation Therapy in Lymphomas
- Questions

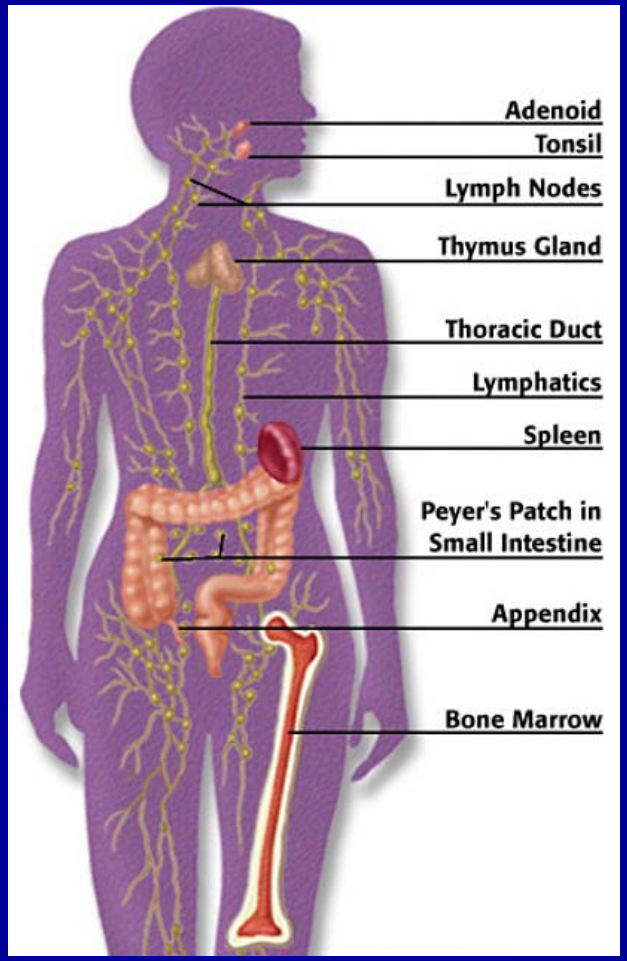
Lymphoma: *Terminology*

- Cancer: uncontrolled growth of abnormal cells
  - Neoplasm: new growth
  - Malignant: “acting maliciously”, tending to become progressively worse (vs. benign)
  - Metastatic: ability to spread from one area to another
- Blood cancers
  - Lymphoma (nodal vs. extra-nodal)
  - Leukemia
  - Myeloma
- Lymphoma subtypes
  - Hodgkin lymphoma
  - Non-Hodgkin lymphoma (NHL)
    - B-cell (85%) and T-cell (15%)

Lymphoma:
Blood Elements



Lymphoma:
Lymphatic System



Lymphoma:
Risk Factors

- Causes are unknown for most people
  - Genetic
    - Unclear
    - No strong familial patterns (studies in identical twins)
  - Environmental factors
    - Some chemicals suspected (pesticides/herbicides/benzene)
    - High-dose radiation exposure
  - Immuno-suppression
    - AIDS, post–organ transplant, autoimmune diseases
  - Viral and bacterial infections
    - HTLV-1 virus, EBV, *H. pylori* bacteria, Hepatitis C

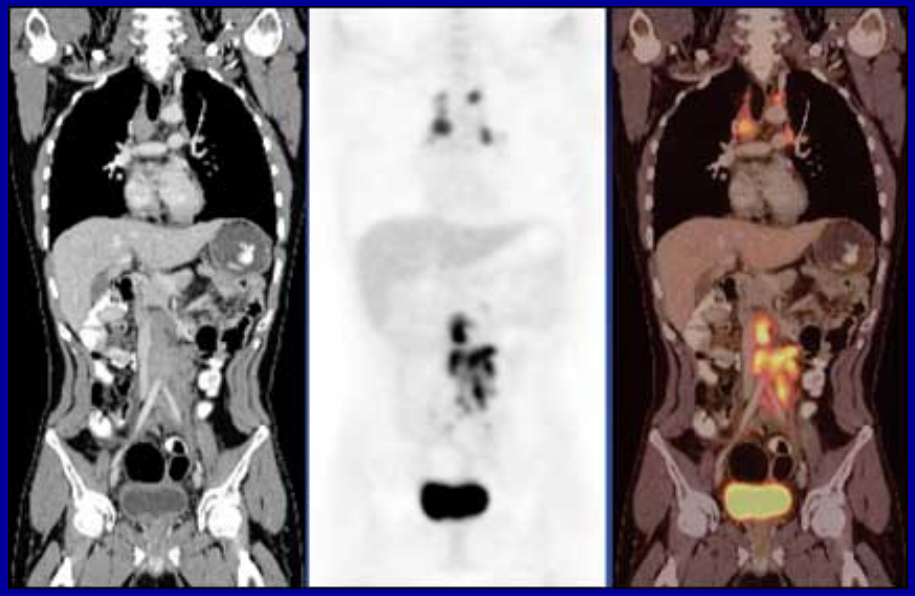
Lymphoma:
Cases

- Case #1
  - 22 year old college student self palpated an enlarged lymph node in the neck, persisted for 3 weeks, otherwise feeling well
- Case #2
  - 72 year old woman with three months of progressive fatigue, night sweats, skin itching and 15 lb weight loss
- Case #3
  - 52 year old man who developed new skin rash on his extremities, fever and enlarged lymph nodes in armpits and groins

Lymphoma:
Diagnosis

- Biopsy
  - Lymph node (needle vs. excision)
  - Other sites (skin, stomach, lung)
- Laboratory studies (blood count, LDH)
- Staging
  - Imaging: CT scan or PET/CT
  - Bone marrow biopsy

PET/CT Scan



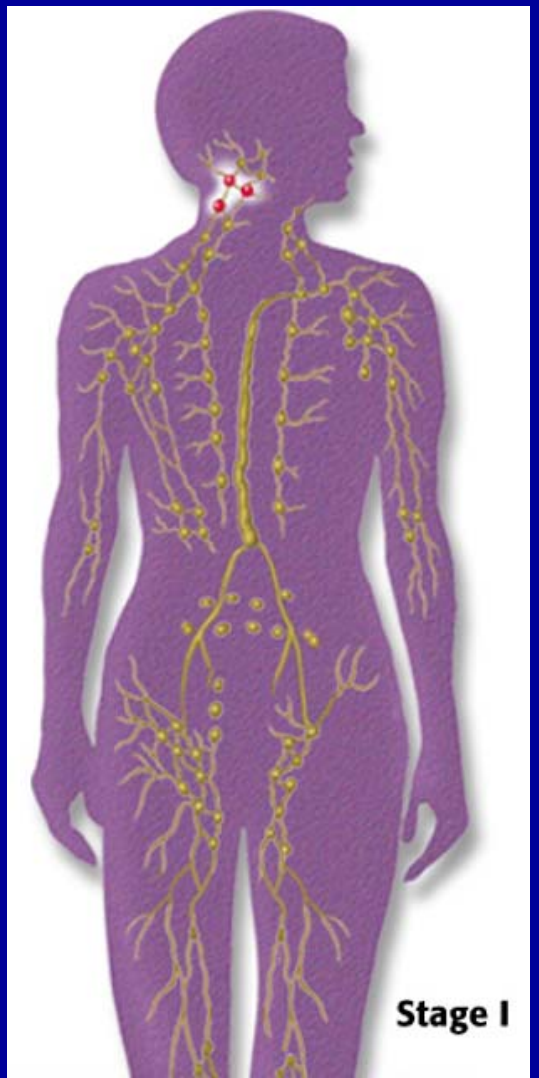
Dual Time Point Imaging PET/CT study (protocol UPCC21408):

- Trying to distinguish between Hodgkin and Non-Hodgkin lymphomas based on the pattern of PET activity

Lymphoma:
Staging

Stage I

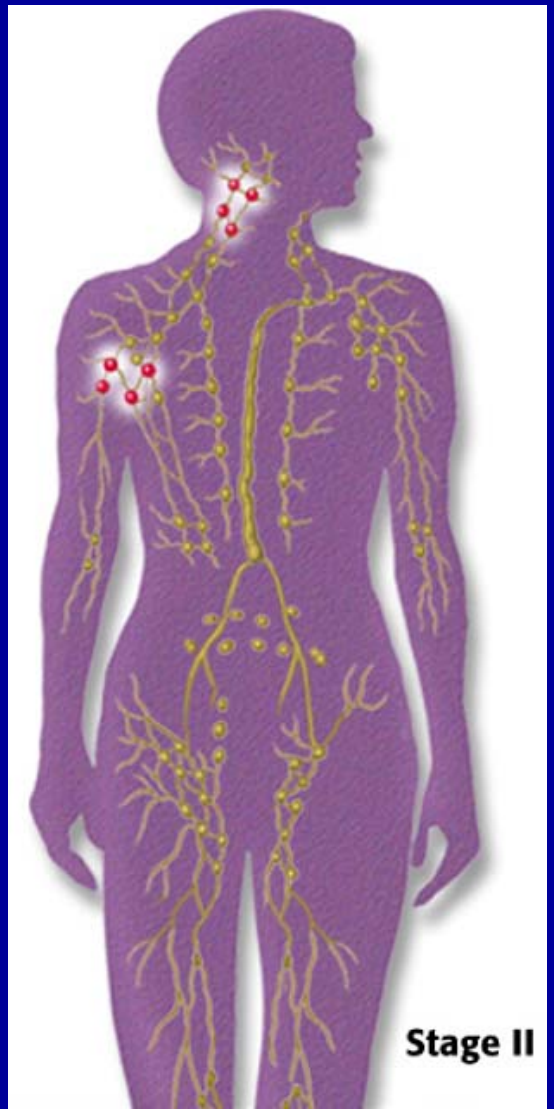
- Localized disease
- Single lymph node region
- Single organ outside the lymph nodes



Lymphoma:
Staging

Stage II

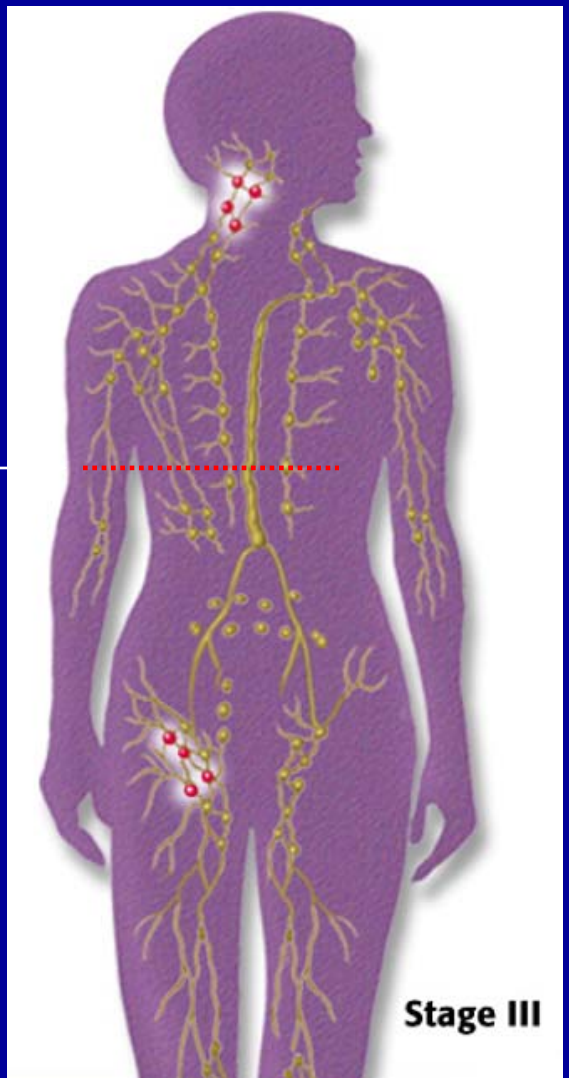
- Two or more lymph node regions near to each other



Lymphoma:
Staging

Stage III

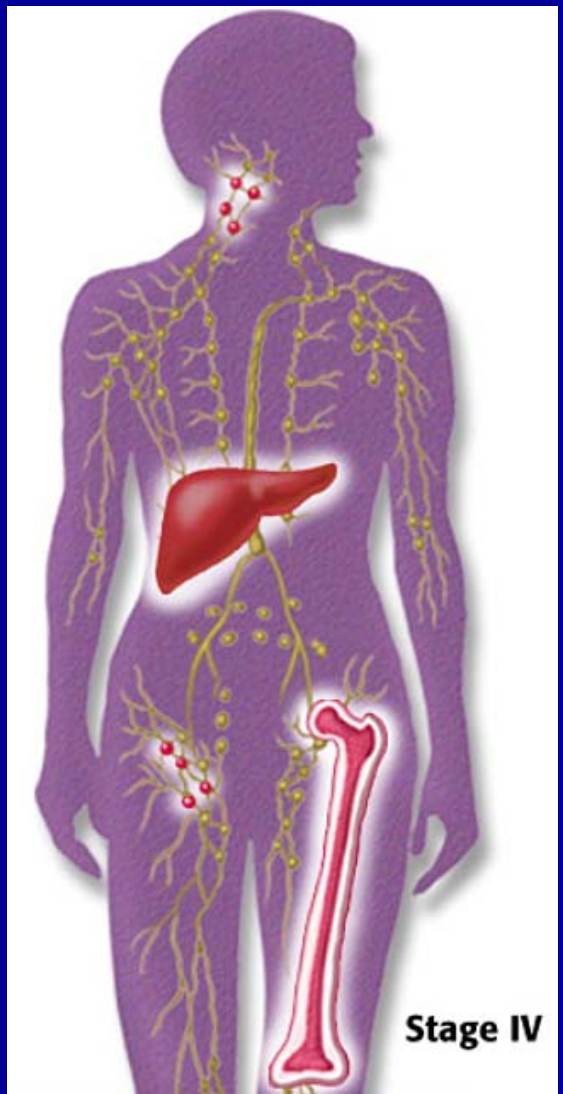
- Two or more lymph node regions above and below the diaphragm



Lymphoma:
Staging

Stage IV

- Widespread disease
- Multiple organs
- With or without lymph node involvement



Lymphoma: *Treatment*

- Important Factors for Consideration
  - Subtype of lymphoma
  - Stage
  - Prognostic characteristics
  - Symptoms
  - Toxicity profile of treatment
  - Other health issues (“co-morbidities”)

Lymphoma:
Treatment

- Chemotherapy
- Radiation
- Combined modality
- Surgery usually not an option
- Bone marrow transplant
  - Autologous
  - Allogeneic
- Novel agents (clinical trials)
- New strategies (vaccines)

Lymphoma:
Chemotherapy

- Destroys cancerous cells by damaging DNA
- Non-cancerous cells in the body are also affected (especially “fast dividing cells” including stem cells in the bone marrow, cell lining of the mouth and gut, hair follicles)

Lymphoma: *Chemotherapy*

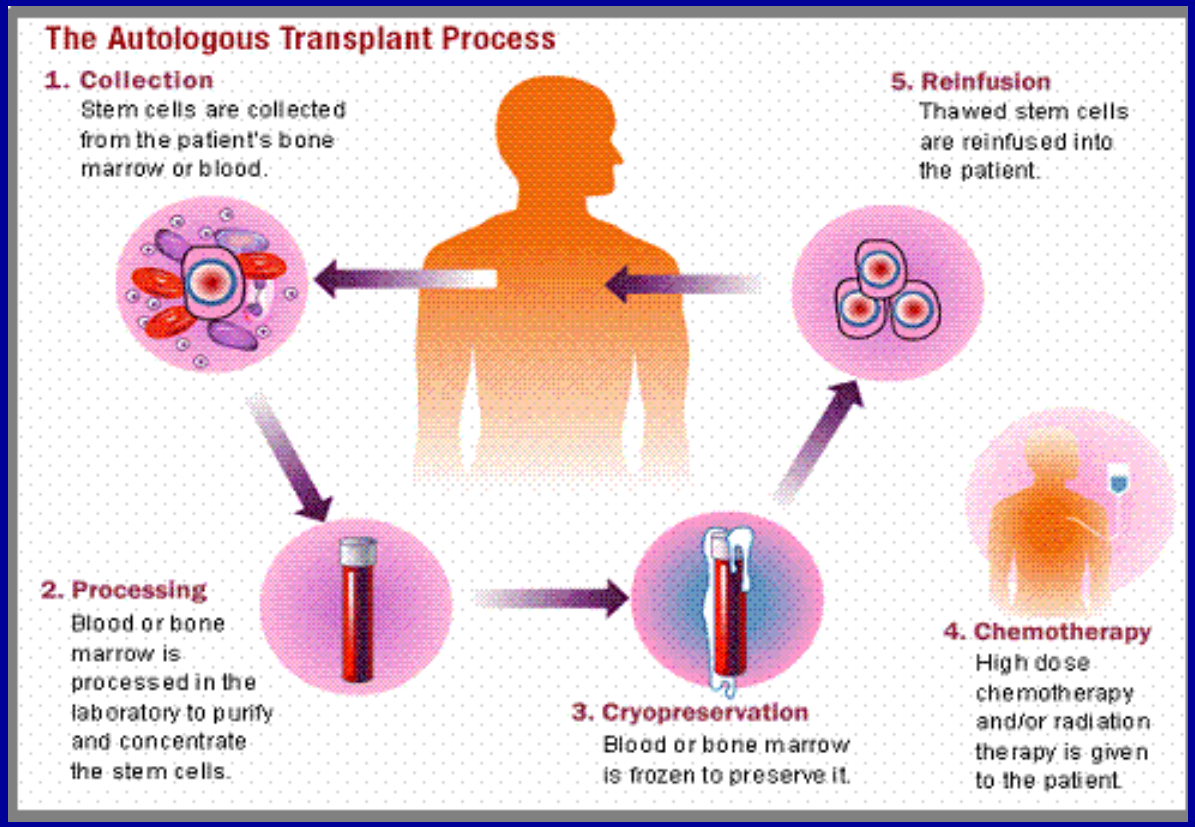
- Short term side effects
  - Fatigue
  - Nausea
  - Low blood counts
  - Hair loss
  - Neuropathy
  - Cognitive changes: “chemo brain”
  - Constipation/diarrhea
  - Mouth ulcers
- Long term side effects
  - Organ impairment (lungs, heart, fertility, bone marrow, peripheral nerves)
  - Secondary malignancies (leukemia, another lymphoma, solid organ cancers)

Lymphoma:
Radiation

- Involved field
- Extensive field
- Dose/intensity
- Different types of radiation source
- Short and long term side effects

Lymphoma:
Bone Marrow Transplant

- Autologous (from patient's own body)
  - Bone marrow (stem cells) is collected from peripheral blood and stored away
  - Patient undergoes high dose chemotherapy (hopefully killing any last lymphoma cell in the body, but it also has profound effect on the stem cells in the bone marrow)
  - Bone marrow is then 'rescued' by infusion of the stem cells back into the body
- Allogeneic (from a donor)
  - Used mostly in leukemias

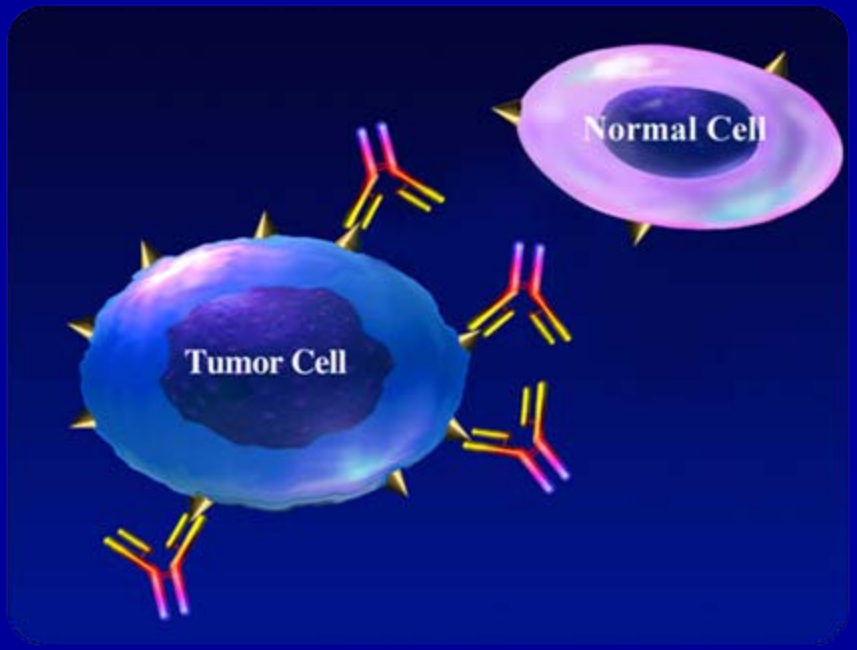

The Autologous Transplant Process
1. Collection
Stem cells are collected from the patient's bone marrow or blood.
5. Reinfusion
Thawed stem cells are reinfused into the patient.
2. Processing
Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.
3. Cryopreservation
Blood or bone marrow is frozen to preserve it.
4. Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient.

Lymphoma:
Research Areas

- Disease
  - Diagnosis
  - Classifications
  - Laboratory research (molecular level)
- Treatment
  - Novel agents (biological and targeted therapies)
  - Optimal length of therapy
- Patient
  - Prognosis
  - Prevention
  - Side effects management
  - Survivorship issues

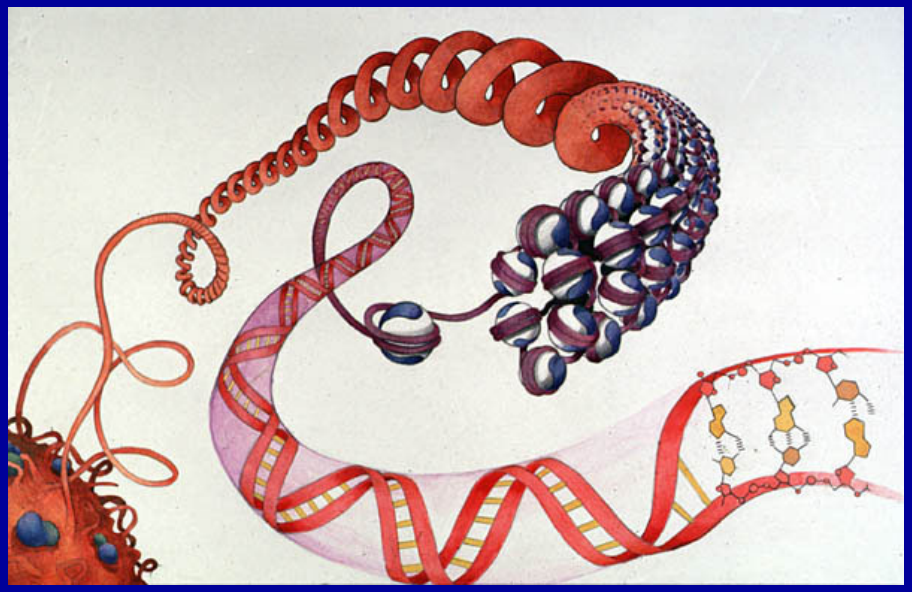
Lymphoma:
Novel Agents

- Monoclonal antibodies
  - Tumor-specific
  - Target proteins on the surface of tumor cells
  - Can deliver chemotherapy, radionucleotide, or toxin directly to the tumor cell



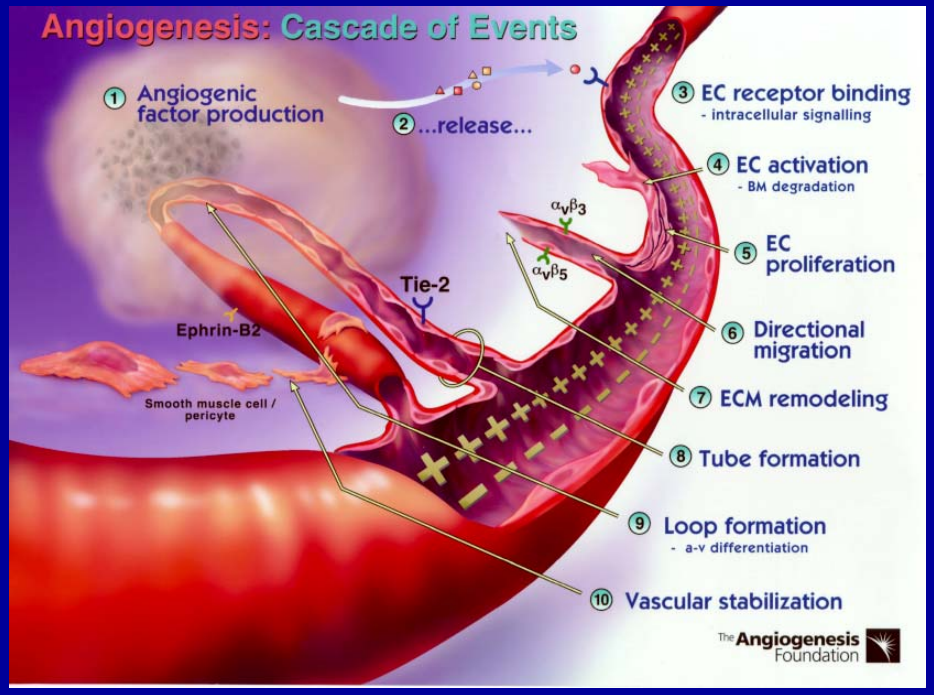
Lymphoma:
Novel Agents

- Histone deacetylase (HDAC) inhibitors
  - interfere with expression of abnormal genes



Lymphoma:
Novel Agents

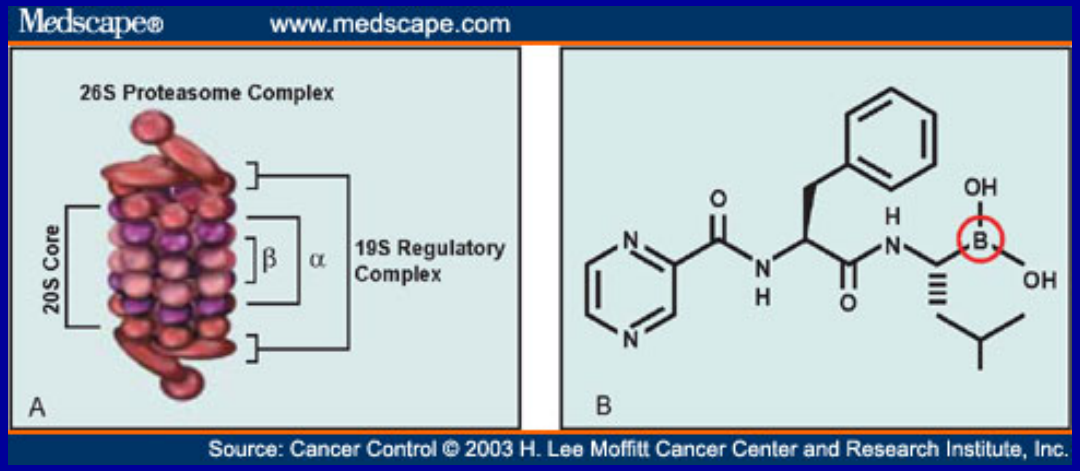
- Immunomodulatory and anti-angiogenic drugs
  - Manipulate immune system
  - Prevent blood vessel formation within the tumor
    - interrupting blood flow to the tumor



www.angio.org/understanding/process.php

Lymphoma:
Novel Agents

- Proteasome inhibitors
  - Stop cell division
    - Block actions of proteasomes (structures inside cells that regulate cell division)



Hodgkin's Disease:
History

Thomas Hodgkin
British physician and pathologist (1798-1866)

Hodgkin Lymphoma: *Classification*

- Hodgkin lymphoma

  – Classical

  -nodular sclerosing

  -mixed cellularity

  -lymphocyte rich

  -lymphocyte depleted

  - Nodular Lymphocyte Predominant (5%)

Hodgkin Lymphoma:
Initial Treatment

- Stage IA and IIA
  - ABVD: abbreviated course of chemotherapy followed by radiation
- Stage III, IV or any stage with B symptoms
  - ABVD: full course of chemotherapy with radiation to areas of bulky disease (>10 cm)

Hodgkin Lymphoma: *Initial Treatment*

- Other regimens for advanced disease:
  - Stanford V
    - adriamycin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone and radiation to initial sites > 5 cm
  - BEACOPP
    - bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone

Hodgkin Lymphoma:
Relapsed Disease Treatment

- High dose (salvage) chemotherapy followed by autologous bone marrow transplant (stem cell rescue)
- Non-cross resistant chemotherapy
- Radiation only
- Clinical trials/novel agents

Hodgkin Lymphoma:
Prognosis Research

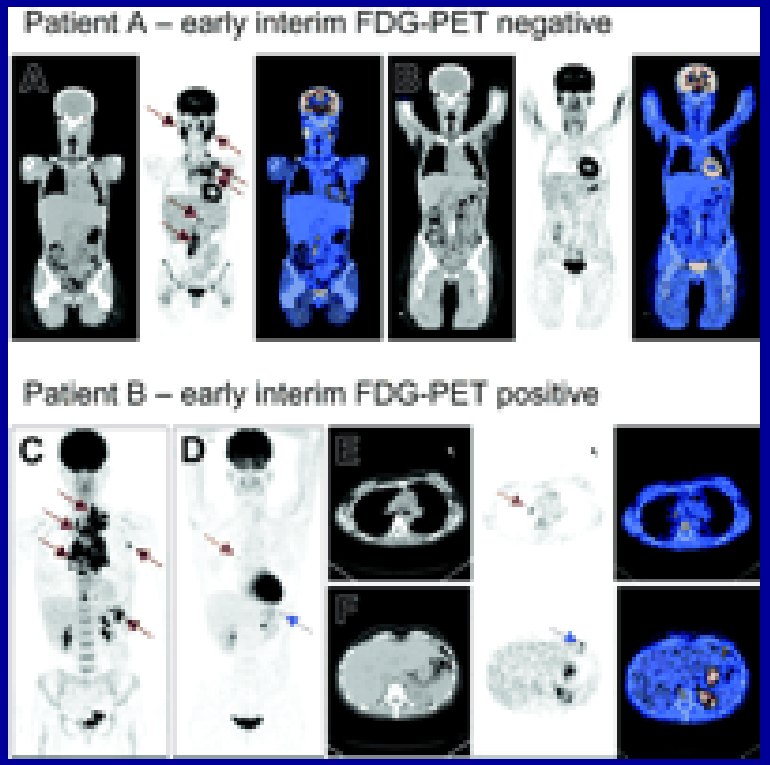
- Prognostic scores
- Early response by imaging
- Gene expression profiling

Hodgkin Lymphoma: *Prognostic Factors*

- Age>45
- Male sex
- Albumin<4
- Hemoglobin<10
- Stage IV
- Leukocytosis
- Lymphopenia
- Elevated sedimentation rate
- Large mass within the chest (mediastinum)

Hodgkin Lymphoma: *Prognosis Research*

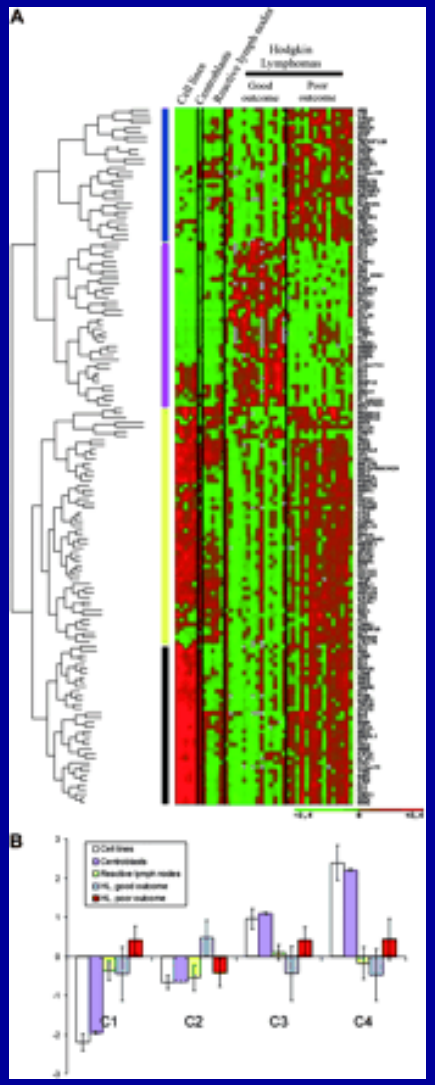
- PET/CT response after two cycles of ABVD
  - Better predictor then traditional prognostic scores
  - Patients with “negative” PET/CT have excellent prognosis
  - Patients with “positive” PET/CT might require more intense therapy then ABVD



Hutchings, M. et al. Blood 2006;107:52-59

Hodgkin Lymphoma:
Prognosis Research

- Gene expression profiling
  - Detects DNA changes in each individual tumor
  - Might predict response to specific chemotherapy regimens
  - Will allow to “tailor” the therapy for each individual



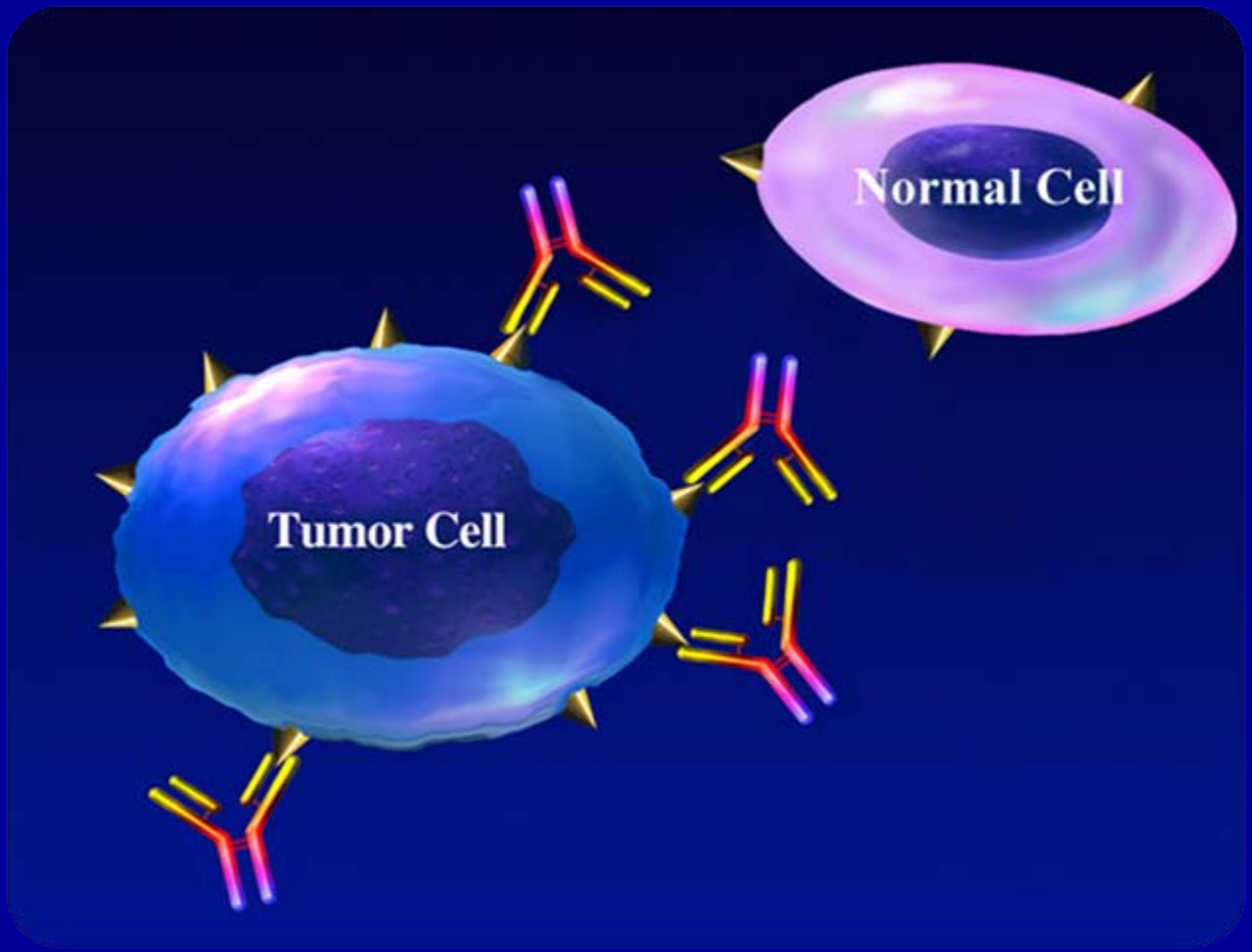
Hodgkin Lymphoma:
Novel Agents

- Chemotherapy
  - Bendamustine: “Rebirth of an Old Drug”
  - New combinations of previously used agents (i.e. gemcitabine)

Hodgkin Lymphoma: *Novel Agents*

- Monoclonal antibodies
  - CD30 antibody
  - CD20 antibody
  - CD40 antibody
  - CD80 antibody
  - CD25 antibody

Hodgkin Lymphoma:
Novel Agents

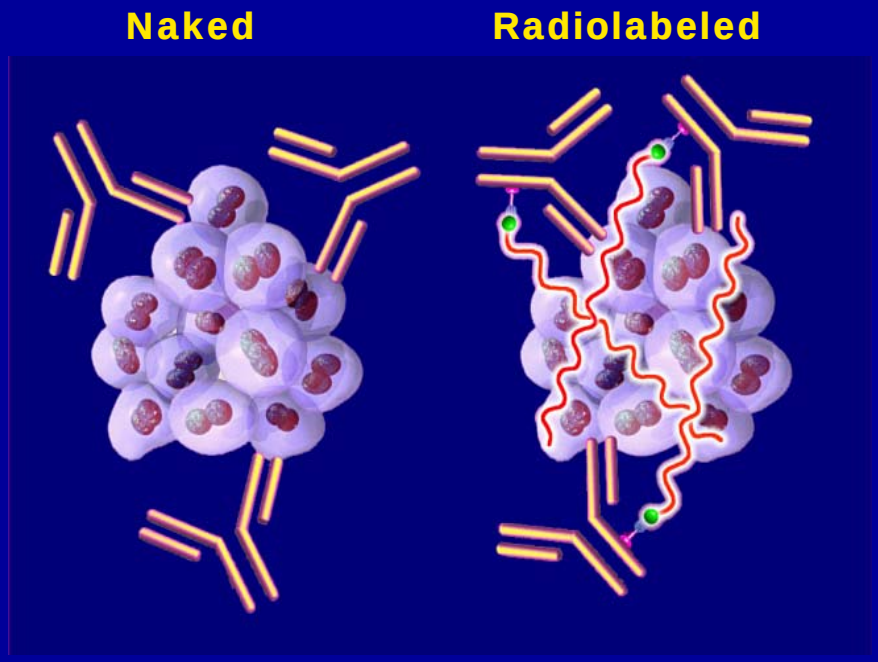


Hodgkin Lymphoma:
Novel Agents

- SGN-35
  - CD30-targeted antibody attached to a potent chemotherapy agent
  - SGN-35 selectively binds to the malignant Hodgkin lymphoma cells, internalizes and releases the chemotherapy inside the cell
  - Early study in 28 patients showed 54% response rate and reduction in tumor size in 93% of patients
  - UPENN plans to open SGN-35 maintenance study for patients with relapsed/refractory Hodgkin lymphoma undergoing stem cell transplant

Hodgkin Lymphoma: *Novel Agents*

- Radioimmunotherapy (RIT)
  - Monoclonal antibody targeting the tumor cells
  - Delivers radiation locally
    - CD25 antibody with radioactive Yttrium in 30 patients: response rate in over 50%



Hodgkin Lymphoma:
Novel Agents

- Histone deacetylase (HDAC) inhibitors
  - Several HDAC inhibitors studied in Hodgkin lymphoma
    - Response rates around 40% in relapsed disease
    - Oral agents
    - Active PANOBINOSTAT trial at UPENN for patients with relapsed Hodgkin lymphoma

Hodgkin Lymphoma: *Novel Agents*

- Immunomodulatory agents with anti-angiogenic properties
  - Lenalidomide
    - Activity in myeloma and some non-Hodgkin lymphomas
    - Phase II trial
      - 12 patients with response rate 33%, well tolerated (ASH 2008)
      - decreasing severity of B symptoms

Hodgkin Lymphoma:
Novel Agents

- Allogeneic bone marrow transplantation (from related or unrelated donor)
  - For young patients relapsing after autologous stem cell transplant
  - Specific toxicities (GVHD)
  - Controversial
  - Possible graft versus lymphoma effect

T cell lymphomas: *Challenges*

- 15% of non-Hodgkin lymphomas
  - Difficult to conduct large clinical trials
- Many subtypes
- Complicated classification
- Less responsive to therapy when compared to B cell lymphomas

T-cell Lymphoma: *WHO classification*

- **Often Leukemic or Disseminated**
  - » T-cell Prolymphocytic Leukemia
  - » T-cell Granular Lymphocytic leukemia
  - » Aggressive NK-Cell leukemia
  - » Adult T-cell Lymphoma/leukemia(HTLV-1+)
  - » Hepatosplenic T-cell Lymphoma
- **Extranodal/Cutaneous**
  - » Extranodal NK/T cell lymphoma, nasal type
  - » Enteropathy-type T-cell lymphoma
  - » Subcutaneous Panniculitis-like Tcell lymphoma
  - » Mucocutaneous $\gamma\delta$ T-cell lymphoma
  - » Mycosis Fungoides
  - » Sezary syndrome
  - » Primary cutaneous anaplastic large cell lymphoma
- **Mainly Nodal**
  - » PTCL, NOS
  - » Angioimmunoblastic T-cell lymphoma
  - » Anaplastic large cell lymphoma

T-cell Lymphoma:
Simplified Classification

- Cutaneous (involving skin)
  - Often followed by dermatology
    - Penn Cutaneous Lymphoma Center (Dr. Rook and Dr. Kim)
    - Local therapies (radiation, creams, photopheresis)
  - Chemotherapy is used when more advanced

- Systemic T cell lymphomas (involving lymph nodes and other organs)
  - Require chemotherapy (plus/minus radiation)
  - Prognosis varies by subtype and other markers

T-cell Lymphoma:
Initial Treatment

- CHOP
- HyperCVAD
- Combined modality (chemotherapy with radiation) for early stage disease
- Autologous bone marrow transplant in first remission is controversial

T-cell Lymphomas: *Relapsed Disease*

- High dose (salvage) chemotherapy followed by autologous stem cell transplant
- Chemotherapy
- Allogeneic bone marrow transplant for relapsed/refractory disease
  - some evidence of graft vs lymphoma effect
- Novel agents

T-cell Lymphoma:
Relapsed Disease

- Pralatrexate (Folotyn)
  - Weekly injections
  - FDA approved specifically for T cell lymphoma in 2009
  - Possible future combinations with other chemotherapy agents
- Gemcitabine alone or in combinations
- Methotrexate

T-cell Lymphoma: *Novel Agents*

- Monoclonal antibody
  - Alemtuzumab: Campath (CD52 antibody)
    - Immuno-suppression and infections
    - Combination studies with CHOP
  - Denileukin diftitox: Ontak (IL-2 antibody)
    - Antibody fused to toxin which is delivered to IL-2 bearing tumor cells leading to cell death
  - SGN-35

T-cell Lymphoma: *Novel Agents*

- HDAC inhibitors
  - Romidepsin
    - Well tolerated
    - About 30% patient responded in early trials
- Proteasome inhibitors
  - Bortezomib (Velcade)
    - In combination with chemotherapy encouraging results

Lymphoma:
Future

- Improvements in diagnosis, more accurate staging
- Gene expression profiling will allow to “tailor” individual therapy (less vs. more intense)
- New “biological”, targeted agents currently in studies will change outcomes of lymphoma
- Novel agents will move to first line therapy
- Novel agents are likely to be used in combination or together with chemotherapy

Lymphoma:
Resources

- www.lls.org
- www.lymphoma.org
- www.clinicaltrials.gov
- www.oncolink.org