Lymphoma

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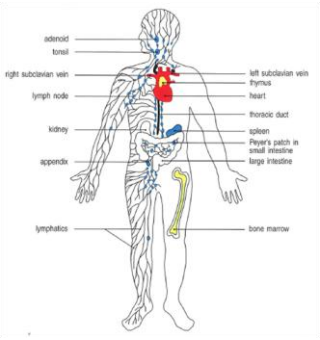
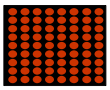
Questions

- What is lymphoma?
- What causes lymphoma?
- What's the difference between the different types?
- Why are treatments so different from person to person? What's the goal of treatment?
- How can we manage side effects of treatment?
- What are some new treatments?
- What does the future hold?

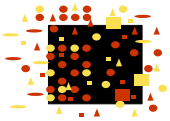
What is Lymphoma?



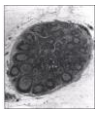
What is Lymphoma?

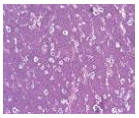


Normal

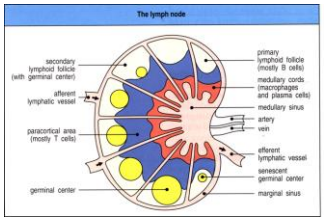


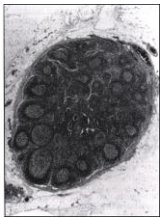
Cancer

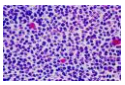


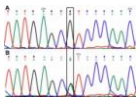


Normal Lymph Node Architecture









WHO Lymphoma Classification

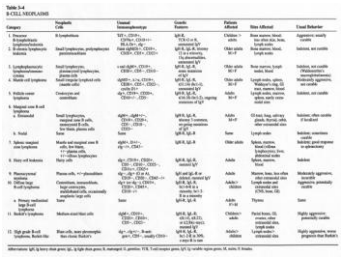


Table 3-4
B-CELL NEOPLASMS

Category	Neoplastic Cells	Usual Immunophenotype	Genetic Features	Patients affected	Sites Affected	Usual Behavior
1. Precursor B lymphoblastic lymphoma/leukemia	B lymphoblasts	TdT+, CD34+, CyMu+, CD10+/−, CD19+, CD22+	IgH, κ, λ TCR γ, δ, β, α, IL-7Rα, IL-7	Children > adults	Bone marrow, blood; less often skin, skin, bone, testis, lymph node	Aggressive; usually curable
2. B-chronic lymphocytic leukemia	Small lymphocytes, prolymphocytes plasmacytoid/lymphoid	Dim sIgM/D+, CD5+, CD20+, CD23+, CD22+	IgH, κ, λ, IgL-R, trisomy 12, 13q deletion, 11q deletion, 17p deletion, mutated IgV	Older adults M > F	Bone marrow, blood, lymph nodes	Indolent, not curable
3. Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia	Small lymphocytes, plasmacytoid lymphocytes, plasma cells	cytoIgM+, CD19+, CD20+, CD5−, CD11c−	IgH, κ, λ, MYD88 exon mutation	Older adults M > F	Bone marrow, lymph nodes, blood	Indolent, not curable (Waldenstrom's macroglobulinemia)
4. Mantle cell lymphoma	Small cleaved lymphoid cells (mantle cells)	sIgM/D+, κ/λ+, CD19+, CD20+, CD5+, CD22+, CD23−	IgH, κ, λ, IgL-R, t(11;14) (bcl-1), mutated IgV	Older adults M > F	Lymph nodes, spleen, Waldeyer's ring, GI tract, bone marrow	Moderately aggressive; not curable
5. Follicle center lymphoma	Centrocytes and centroblasts	sIgG/A+, κ/λ+, CD19+, CD20+, CD10+, −CD23+	IgH, κ, λ, IgL-R, t(14;18) (bcl-2), ongoing mutations of IgV	Adults M > F	Lymph nodes, marrow, spleen, early extranodal sites	Indolent, not curable
6. Marginal zone B cell lymphoma a. Extranodal	Small lymphocytes, marginal zone B cells, monocytoid B cells, plasma cells, blast forms, plasma cells	sIgM+, −IgM++, CD19+, CD20+, CD22+, CD5−, CD10−, CD23−	IgH, κ, λ, IgL-R, trisomy 3, mutations, ongoing mutations of IgV	Adults M > F	GI tract, lung, salivary glands, thyroid, orbit, other extranodal sites	Indolent; often curable if localized
b. Nodal	Same	Same	IgH, κ, λ, IgL-R	Same	Lymph nodes	Indolent; sometimes aggressive; usually good response to splenectomy
7. Splenic marginal zone lymphoma	Mantle and marginal zone B cells, few blasts, plasmacytoid cells, +/− plasma cells, villous lymphocytes, hairy cells	sIgM+, D++, cIg−/+, CD42−	IgH, κ, λ, IgL-R	Older adults	Spleen, marrow, blood (villous lymphocytes), liver, lymph nodes, rarely lungs, marrow	Indolent
8. Hairy cell leukemia	Hairy cells	sIgG/A+, CD19+, CD20+, CD22+, CD25+, CD103+, CD5−	IgH, κ, λ, IgL-R, mutated IgV	Adults	Spleen, marrow, blood	Indolent
9. Plasmacytoid myeloma	Plasma cells, +/− plasmablasts	IgG and IgA, κ or λ restricted, mutated IgV	IgH and IgL-R or related, mutated IgV	Adults	Marrow, bone, less often other extramedullary sites	Moderately aggressive, incurable
10. Diffuse large B cell lymphoma	Centroblasts, immunoblasts, centroblasts, multilobated cells, occasionally anaplastic large cells	sIgG/M+, κ/λ+, CD19+, CD20+, CD45+, −CD43+, CD10−/+	IgH, κ, λ, IgL-R, t(3;14), mutations, mutations in 5-3 5 or a minority	Adults > children	Lymph nodes and extranodal sites (GI tract, skin, CNS, bone, testis)	Aggressive, potentially curable
a. Primary mediastinal large B cell lymphoma	Same	Same	IgH, κ, λ, IgL-R	Adults F > M	Thymus	Same
11. Burkitt's lymphoma	Medium-sized blast cells	sIgM+, CD19+, CD20+, CD38+, CD10+, −CD22+	IgH, κ, λ, IgL-R, t(8;14), t(2;14), or t(22;8) myc, mutations of IgV	Children > adults	Facial bones, GI, ovaries, other extranodal sites, bone marrow, blood	Highly aggressive; potentially curable
12. High grade B cell lymphoma, Burkitt-like	Blast cells, some pleomorphic; then classic Burkitt's	sIg+, cIg+/−, B-antigen+, CD19+, usually CD10+	IgH, κ, λ, IgL-R, t(8;14), t(2;8), or 8;22), myc, 11q deletion	Adults > children	Lymph nodes > extranodal sites	Highly aggressive, worse prognosis than Burkitt's

Abbreviations: IgH, Ig heavy chain genes; IgL, Ig light chain genes; B, mutatagenic V, genetics; TCR, T cell receptor genes; IgV, Ig variable region genes; M, males; F, females.

WHO Lymphoma Classification

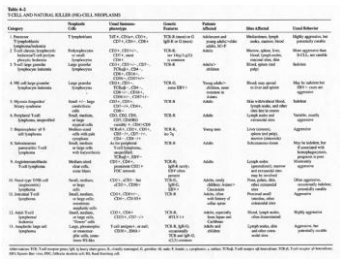


Table 4-2
T-CELL AND NATURAL KILLER (NK)-CELL NEOPLASMS

Category	Neoplastic Cells	Usual Immunophenotype	Genetic Features	Patients affected	Sites Affected	Usual Behavior
1. Precursor T lymphoblastic lymphoma/leukemia	T lymphoblasts	TdT+, CD1a+, CD2+, CD7+, CD5+, CD8+	TCR β (most) or γ IgH (8 of 12 cases)	Adolescent and young adults > children, M > F	Mediastinum, lymph nodes, marrow, blood	Highly aggressive, but potentially curable
2. T-prolymphocytic leukemia/T cell prolymphocytic leukemia	Prolymphocytes or small lymphocytes	CD3+, CD5++, CD7+, mature T cell phenotype	TCR β, inv 14q (q32) is common	Adults	Marrow, spleen, liver, blood, lymph nodes, mucosal sites, skin	More aggressive than B-CLL, not curable
3. T-cell large granular lymphocyte leukemia	Large granular lymphocytes	CD2+, CD3+, CD5+, CD7+, TCRαβ+, CD4−, CD8+, CD16+, CD56+, CD57+	TCR β	Adults > children	Marrow, blood, liver, spleen, lymph nodes	Indolent
4. NK cell large granular lymphocyte leukemia	Large granular lymphocytes	CD2+, CD3−, CD5−, TCRαβ−, CD8−, CD16+, CD56+, CD57+/−	TCR γ, some IDH1+	Young adults > children, some Asian ancestry	Blood, may spread to liver and spleen	May be indolent but IDH1+ cases are aggressive
5. Mycosis fungoides/ Sézary syndrome	Small +/− large cerebriform cells	CD3+, CD4+, CD5+, CD7+, CD8−	TCR β	Adults	Skin with blood, blood, lymph nodes, other sites	Indolent
6. Peripheral T-cell lymphoma, unspecified	Small, medium, large cerebriform or regular cells	CD3, CD5, CD6, CD7, CD4+/−, variable +/− CD8+/CD4	TCR β	Adults	Lymph nodes and extranodal sites	Variable, usually aggressive
7. Hepatosplenic γ/δ T cell lymphoma	Medium-sized blast cells, sinusoidal cytoplasm	TCR γ/δ+, CD2+, CD3+, CD5−, CD7+/−, CD8−/+	TCR γ, 6q−/7q−	Young men	Liver (sinusoids), spleen, marrow (sinusoids), GI (sinusoids)	Aggressive
8. Subcutaneous panniculitis-like T cell lymphoma	Small, medium, large cells with karyorrhexis	As for peripheral T cell lymphoma, unspecified, but CD8+	TCR β	Adults	Skin	May be indolent, but if associated with hemophagocytosis, prognosis is poor; usually aggressive
9. Angioimmunoblastic T-cell lymphoma	Medium-sized clear cells, some blasts	CD2+, CD3+, CD5+, CD4+, processed CD1+ FDC network	TCR γ, IgH κ/λ (early), EBV often	Adults	Lymph nodes (generalized), marrow (sometimes), liver, spleen, may be involved	
10. Nasal type EVB cell neoplasm/ NK cell lymphoma	Small, medium, or large cells	CD2+, CD3−/+, but sIg−, CD56+, CD16−/+, CD8+	TCR γ, IgH κ/λ, EBV+	Adults, rarely children, Asian?	Nose, palate, skin, testis, other sites	Often aggressive, occasionally indolent, potentially curable
11. Intestinal T-cell lymphoma	Small, medium, large cerebriform, regular cells, sometimes multilobate cells	CD3+, CD8+/−, CD4−, CD56+/−	TCR β	Adults, often Scandinavian, of celiac sprue	Proximal small intestine, other extranodal sites	Aggressive
12. Adult T-cell lymphoma/ leukemia	Small, medium, or large cells, cerebriform	CD3+, CD4+, CD25+/−, CD8−/+	TCR β, HTLV+	Adults, especially from Japan and Caribbean	Blood, lymph nodes, often disseminated	Highly aggressive
13. Anaplastic large cell lymphoma	Large pleomorphic or immunoblastic cells, often with hallmark cells	T cell antigens+, no sIg, CD30+, CD60+	TCR β, IgH κ/λ occasionally TCR γ or IgH κ/λ, t(2;5)(p23;q35)	Adults and children	Lymph nodes, skin and other extranodal sites	Aggressive, but potentially curable

Abbreviations: TCR, T cell receptor genes; IgH, Ig heavy chain genes; B, clonally rearranged; D, germline; M, male; F, female; c, cytoplasm; s, surface; TCRαβ, T cell receptor αβ heterodimer; TCRγδ, T cell receptor γδ heterodimer; HTLV, human T cell lymphotropic virus; EBV, Epstein Barr virus; FDC, follicular dendritic cell; RS, Reed-Sternberg cell.

Some Lymphoma Subtypes

- Diffuse large B cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma
- Peripheral T cell lymphoma
- Hodgkin Lymphoma
- More than 45 different types all together

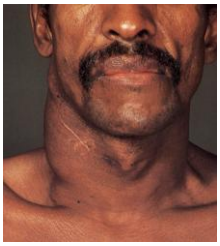
Basic Categories of Lymphomas

Grade	Extent at Diagnosis	Rate of Growth	Response to Treatment
Low	Widespread	Slow	Excellent but hard to cure
Intermediate	Localized or widespread	Rapid	Excellent, often curable
High	Widespread	Extremely rapid	Excellent, often curable

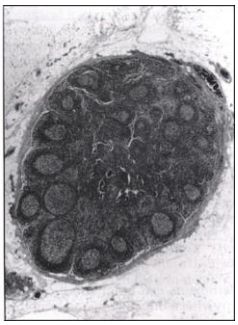
Why does a person get lymphoma?

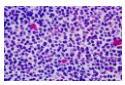
- Very difficult to tell in an individual case
- Possible risk factors
  - Various chemicals, esp. pesticides
  - Previous chemotherapy or radiation
  - Certain viruses
  - Immune deficiency
  - Rarely hereditary component
- Molecular basis of lymphoma much better understood
- Might be possible to answer this question for individuals in the not-so-far off future

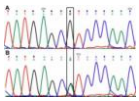
Case Presentation



What Type of Lymphoma?
Biopsy







WHO Lymphoma Classification

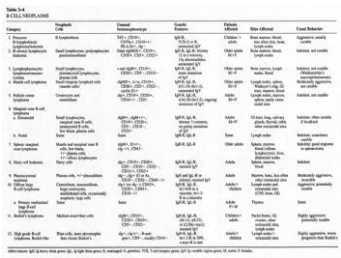


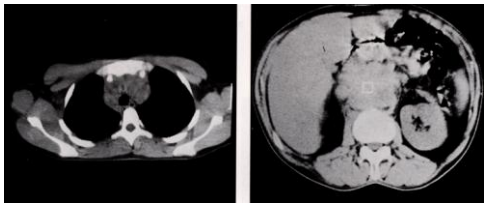
Table 3-4
B-CELL NEOPLASMS

Category	Neoplastic Cells	Usual Immunophenotype	Genetic Features	Patients Affected	Sites Affected	Usual Behavior
1. Precursor lymphoblastic lymphoma/leukemia	B lymphoblasts	TdT+, CD10+, CD19+, CD22+, CD34+/−, HLA-DR+, cIg+	IgH/IL-3 rearrangement; IgV/IL-3 inversion; IgV/IL-3/p.ter. translocation; 11q aberrations; mutated IgV genes	Children > adults	Bone marrow, blood, lymph nodes, brain, liver, spleen, testes, thymus	Aggressive; usually curable
2. B-chronic lymphocytic leukemia	Small lymphocytes, prolymphocytes, paraimmunoblasts	sIgM+, sIgD+, CD5+, CD23+, CD38+, CD43+, CD22+	Frequent IgV mutations; 13q deletion; 11q deletion; 17p deletion; 12q trisomy; mutated IgV genes	Older adults 3/1–5/1	Bone marrow, blood, lymph nodes	Indolent, not curable
3. Lymphoplasmacytic lymphoma/Waldenstrom's Macroglobulinemia	Small lymphocytes, plasmacytoid lymphocytes, plasma cells	sIgM+, sIgD+/−, CD19+, CD20+, CD38+, CD43+, CD22+, CD5−/+, CD23−, CD10−, CD138+	Frequent IgV mutations; mutated IgV genes	Older adults 3/1–5/1	Bone marrow, lymph nodes, blood	Indolent, not curable (Waldenstrom's macroglobulinemia); occasionally aggressive, not curable
4. Mantle cell lymphoma	Small to medium lymphoid cells (mantle cells)	sIgM3+/−, κ/λ+, CD19+, CD20+, CD22+, CD5+, CD23−, CD10−/+, CD138−	t(11;14)(q13;q32); mutated IgV genes	Older adults 3/1–5/1	Lymph nodes, spleen, Waldeyer's ring, GI tract, marrow, blood	Aggressive; not curable
5. Follicle center lymphoma	Centrocytes and centroblasts	sIgM+/−, sIgD−, CD19+, CD20+, CD10+/−, CD23−/+	t(14;18)(q32;q21); mutation of IgV	Adults 3/1–5/1	Lymph nodes, spleen, adipose, testes, rarely extra-nodal sites	Indolent, not curable
6. Marginal zone B-cell lymphoma						
a. Extranodal	Small lymphocytes, marginal zone B cells, lymphoplasmacytoid cells, low blasts, plasma cells	sIgM+, sIgD−/+, CD19+, CD20+, CD22+, CD5−, CD10−, CD23−, CD11c−/+	IgH/IL-3/p.ter. aberrant 3 translocation; 11q aberrations; mutated IgV genes	Adults 3/1–5/1	GI tract, lung, salivary glands, thyroid, orbit, other extranodal sites	Indolent; often curable if localized
b. Nodal	Same	Same	IgH/IL-3/p.ter.	Same	Lymph nodes	Indolent; sometimes aggressive
7. Splenic marginal zone lymphoma	Marginal zone B cells, few blasts, plasmacytoid cells, 11+ villous lymphocytes	sIgM+, CD19+, CD20+, cIg−/+, CD43−, CD5−, CD23−, CD11c+	IgH/IL-3/p.ter.	Older adults	Spleen, marrow, blood (villous lymphocytes), lymph nodes, abdominal nodes	Indolent; good response to splenectomy
8. Hairy cell leukemia	Hairy cells	sIgG+, CD19+, CD20+, CD22+, CD11c+, CD103+, CD25+, CD123+, CD5−, CD10−, CD23−, CD11b−/+	IgH/IL-3/p.ter.; mutated IgV	Adults	Spleen, marrow, blood	Indolent
9. Plasmacytoid dendritic cell neoplasm	Plasma cells, +/− plasmablasts	sIgM+/−, sIgD−, CD19−, CD20−, CD22−, CD38+, CD138+, CD45−/+, CD56+/−	IgH and IgL; IR or IgV rearrangement; mutated IgV	Adults	Marrow, bone, bone marrow, lymph nodes, other sites	Moderately aggressive, usually curable
10. Diffuse large B-cell lymphoma	Centroblasts, immunoblasts, large centrocytes, Reed-Sternberg, occasionally anaplastic large cells	sIgM+/−, κ/λ+, CD19+, CD20+, CD22+, CD45+/−, CD10−/+	IgH/IL-3/p.ter.; IgH/IL-3/p.ter. or IgH/IR translocations; 3q aberrations; mutated IgV genes	Adults > children	Lymph nodes and extranodal sites (GI, bone, CNS)	Aggressive, potentially curable
a. Primary mediastinal (thymic) B-cell lymphoma	Same	Same	IgH/IL-3/p.ter.	Adults 3/1–5/1	Thymus	Same
11. Burkitt's lymphoma	Medium-sized blast cells	sIgM+, CD19+, CD20+, CD22+, CD10+, CD38+, CD77+, CD43−, CD5−, CD23−	IgH/IL-3/p.ter.; t(8;14), t(8;22), t(2;8); mutated IgV genes	Children > adults	Facial bones, GI, ovaries, other extranodal sites, lymph nodes	Highly aggressive; potentially curable
12. High grade B-cell lymphoma, Burkitt-like	Blast cells, some pleomorphic like (from Burkitt's)	sIgM+/−, κ/λ+/−, B-antigen+, CD19−, CD20−, CD10−/+	IgH/IL-3/p.ter.; IgH/IR; mutated IgV genes	Adults > children	Lymph nodes > extranodal sites	Highly aggressive, worse prognosis than Burkitt's

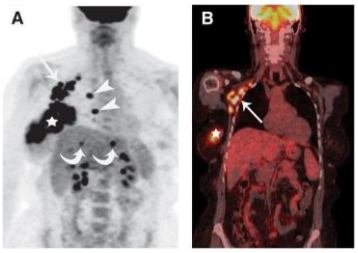
Abbreviations: IgH, Ig heavy chain gene; Ig, Ig light chain genes; B, antigenic; G, germline; TTR, T-cell receptor genes; IgV, Ig variable region genes; IR, entire; D, breaks.

- Diagnosis: Exactly which subtype of NHL the patient has.
- Staging: How much disease is there?

Staging with CT Scans



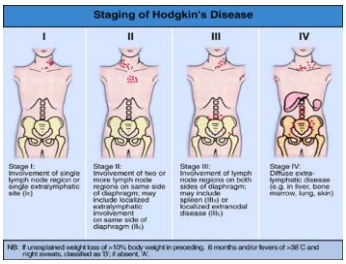
Staging with PET Scans



Staging: Bone Marrow Biopsy

This person has just learned that she gets to have a bone marrow exam

Ann Arbor Staging System



What is the Prognosis?

- Subtype of lymphoma
- Extent of disease
  - Stage
  - “extranodal sites”
  - LDH
- Patient’s status
  - Age
  - “performance status”

Tools for Treating Lymphoma

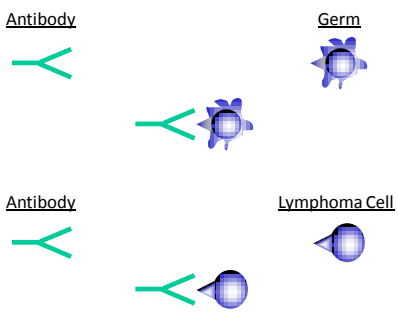
- Surgery
- Radiation
- Chemotherapy
- Antibodies
- Newer treatments

Surgery

Radiation

Chemotherapy

Antibodies

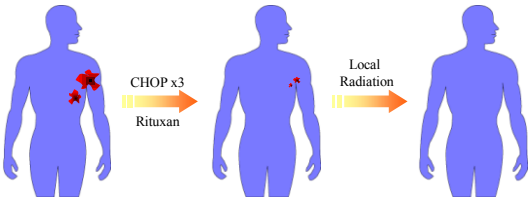


Lymphoma: Goals of Treatment

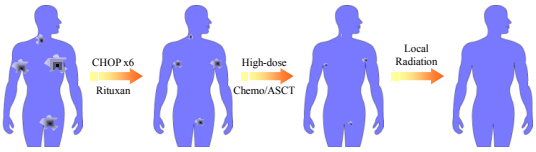
Depends on the type of lymphoma

- Cure – aggressive treatment needed
- Cure – really aggressive treatment needed
- Hard to cure—treat as a chronic disease
- Try to determine the most appropriate role for experimental therapy

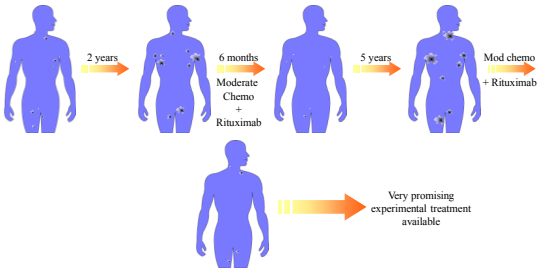
Curing Localized NHL (Diffuse Large B-Cell) With Aggressive Treatment



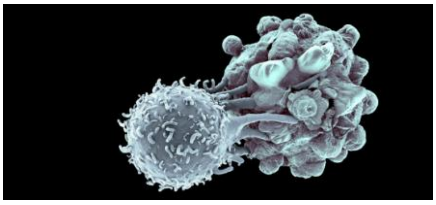
Curing Advanced Diffuse Large B-Cell Lymphoma With Aggressive Treatment



Treating Low-Grade Lymphoma (Such as Follicular Lymphoma) as a Chronic Disease

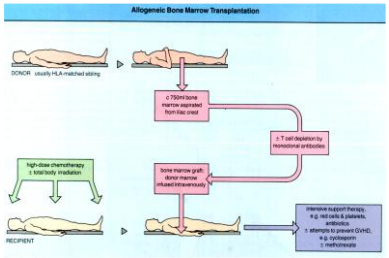


Harnessing the Immune System to Battle the Worst Lymphomas



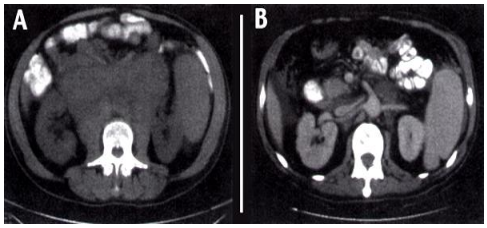
Harnessing the Immune System

Donor T-cell/stem cell transplants



New Treatments

Donor T-cell/stem cell transplants



Toxic Side-Effects

Most current treatments affect normal tissues too

- Bone marrow—risk of infection, anemia
- Hair loss
- Nausea and vomiting
- Mouth sores
- Neuropathy
- Less common but very serious
  - Heart toxicity
  - Secondary cancers
- The strongest therapy (transplant) has major side effects

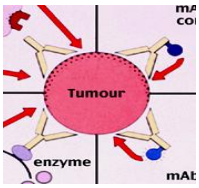
Current Status

- We are doing very well with most lymphomas
- But current therapies are too non-specific and therefore toxic!
- Huge advances are coming down the pike right now
  - Harnessing the immune system
  - Better understanding of lymphoma
  - Figuring out and targeting the Achilles' heel of cancers

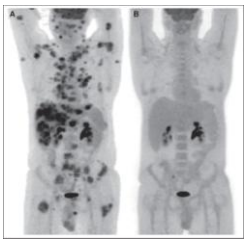
Harnessing the Immune System

New Antibodies

- Hodgkin Lymphoma:
  - Target: CD30
  - Antibody: Brentuximab
- B cell lymphomas
  - Target: CD22
  - Antibody: Inotuzumab
  - Target: CD20
  - Antibody: Rituximab, new ones
- Many others

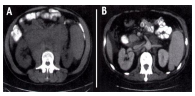


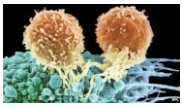
Harnessing the Immune System
New Antibodies

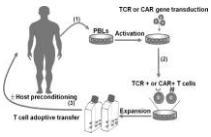


Brentuximab (targeting CD30) in anaplastic CD30+ T cell lymphoma

Harnessing the Immune System
Engineering Tumor Specific T- Cells

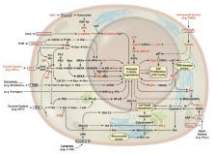




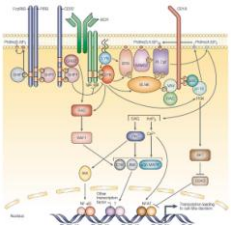


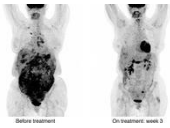
Figuring Out and Targeting the Achilles' Heels of Lymphomas

- Understand better what is driving a lymphoma
  - Abnormalities in molecular circuitry that drive the disease
- Develop strategies to interfere with the molecular circuitry



Targeting Lymphoma Achilles' Heel
BTK inhibitors





Many other molecular-targeted drugs in development

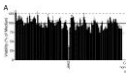
The Cutting Edge:
Personalized Lymphoma Therapy

Genomic Analysis

- **Exome Sequencing**
- **RNA Seq**

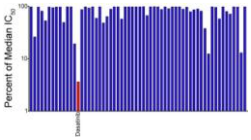
Functional Analysis

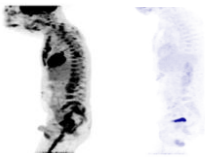
In vitro
- **RNAi**
- **Compound screen**



Analysis → Choosing the Right Drug

Individualized Achilles' Heel-Based Treatment
Targeting T-lymphoblastic Lymphoma





Summary

- We know a lot about lymphoma and our treatments are very effective
  - Low grade lymphomas hard to cure but usually very controllable
  - More aggressive lymphomas frequently cured
- But:
  - Treatments are too non-specific and thus toxic
  - Despite many successes there are too many failures
- Lymphoma medicine is in the midst of a revolution
  - Harnessing the immune system
    - Reduced intensity allogeneic transplants
    - New antibodies
    - Engineered T-cells
  - Identifying and targeting Achilles' heels—personalized medicine
    - Many new targeted drugs in development
    - Technology being developed for wide application