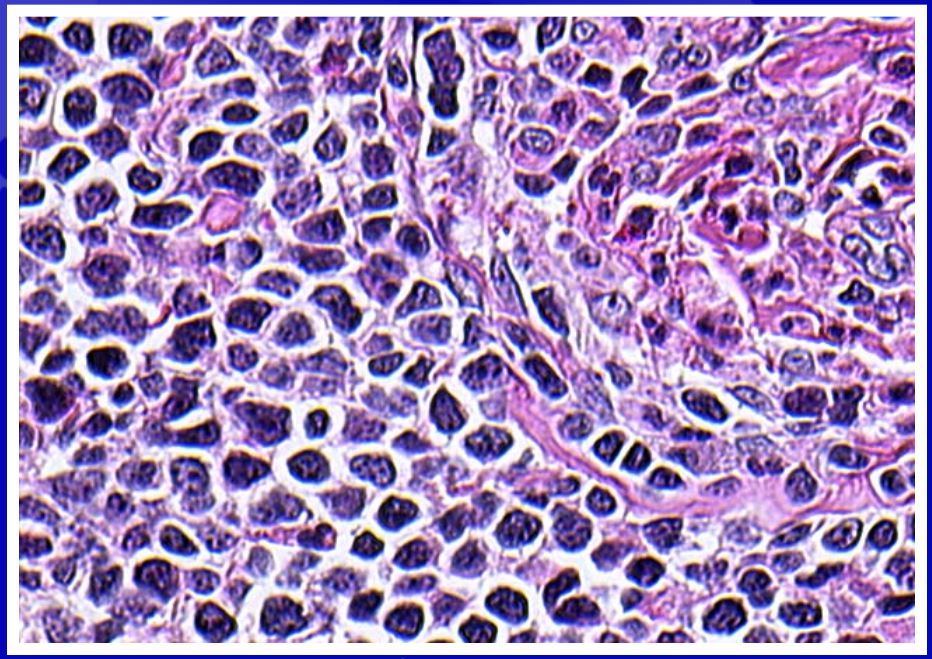
Dr. Ronan Foley

Lymphoma: Understanding the basics

Non-Hodgkin's Lymphoma Fundamentals

Understanding the Basics



Disclosures Ronan Foley

- **Advisory Boards**: Roche Canada, Lundbeck Canada, Sanofi, Celgene, Pfizer Oncology, Novartis, Jansen, Alexion
- **Lectures:** Hoffmann-LaRoche Ltd., Lundbeck Canada, Sanofi, Celgene, Pfizer Oncology, Novartis, Jansen
- **Funding:** Roche Canada

Outline

- Introduction
- Biology
- Diagnosis and Staging
- Treatment
- New Appraoches

The War on Cancer

Lymphomas and Lymphocytes

- NHLs originate in the bone marrow, lymph nodes or lymphatic organs
- Lymphocytes normally circulate to other parts of the body
- Lymphoma cells (abnormal lymphocytes) may have spread upon diagnosis and may be found in many sites of the body

Zinzani PL. *Semin Oncol* 2005;32(Suppl 1):S4-S10.

NHL

- Malignant disease of lymphoid tissue
- Caused by abnormal growth of B- or T-lymphocytes
  - Eventually form tumors and/or circulate in the blood
- Determining B-cell or T-cell involvement is crucial to diagnosis, treatment and outcome
- B-cell lymphomas comprise 90% of all NHL cases; T-cell neoplasms 10%

Armitage JO. *CA Cancer J Clin* 2005;55:368-76.
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.

Overview

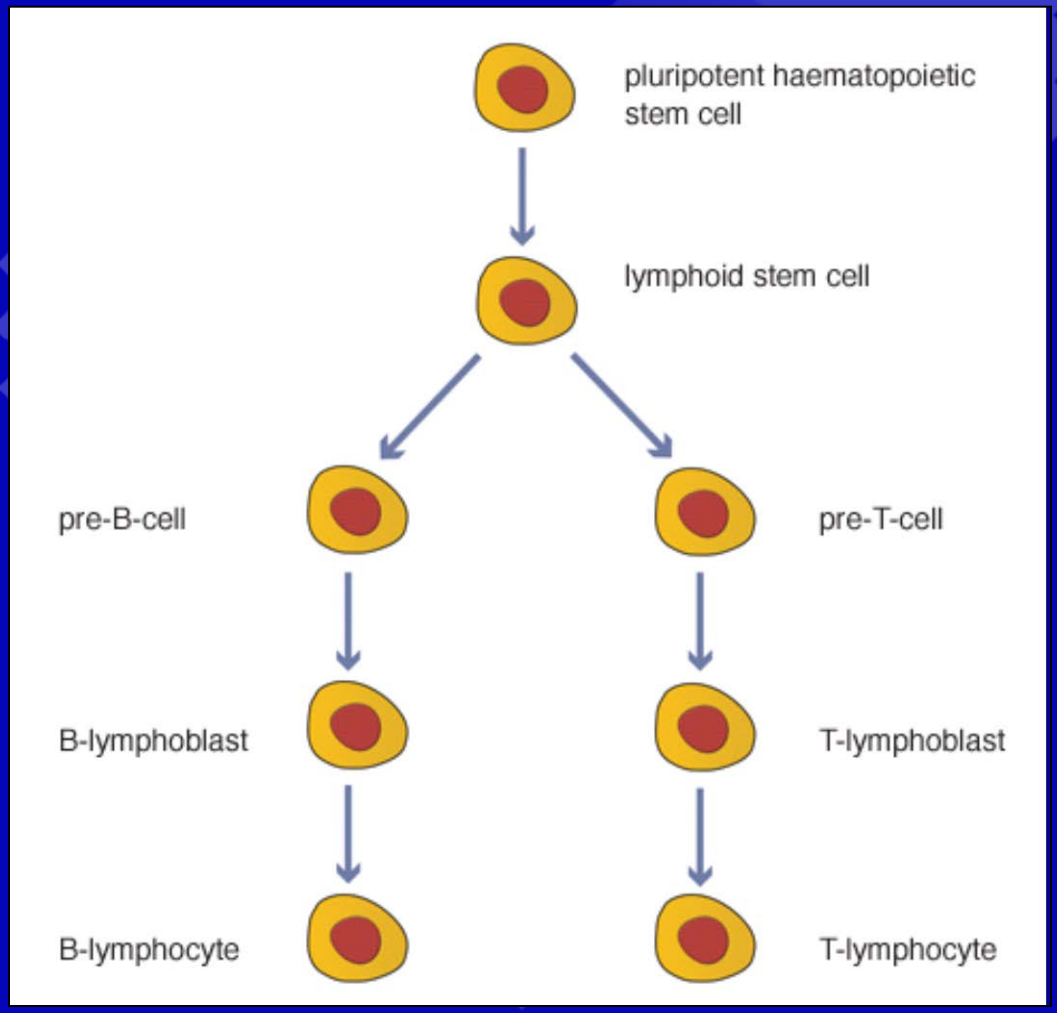
Symptoms such as fever, weight loss and night sweats are the common presenting symptoms of NHL, as are enlarged glands (nodes), which are usually painless.

Accurate diagnosis is critical to assessing treatment options:

- **Biopsy is ordered upon suspicion of cancer**
- **Diagnosis is made by hematopathologic study of excised tissue (lymph nodes), including the use of flow cytometry**
- **Methods of diagnosis are evolving (e.g., increasing use of molecular techniques and cytogenetics)**

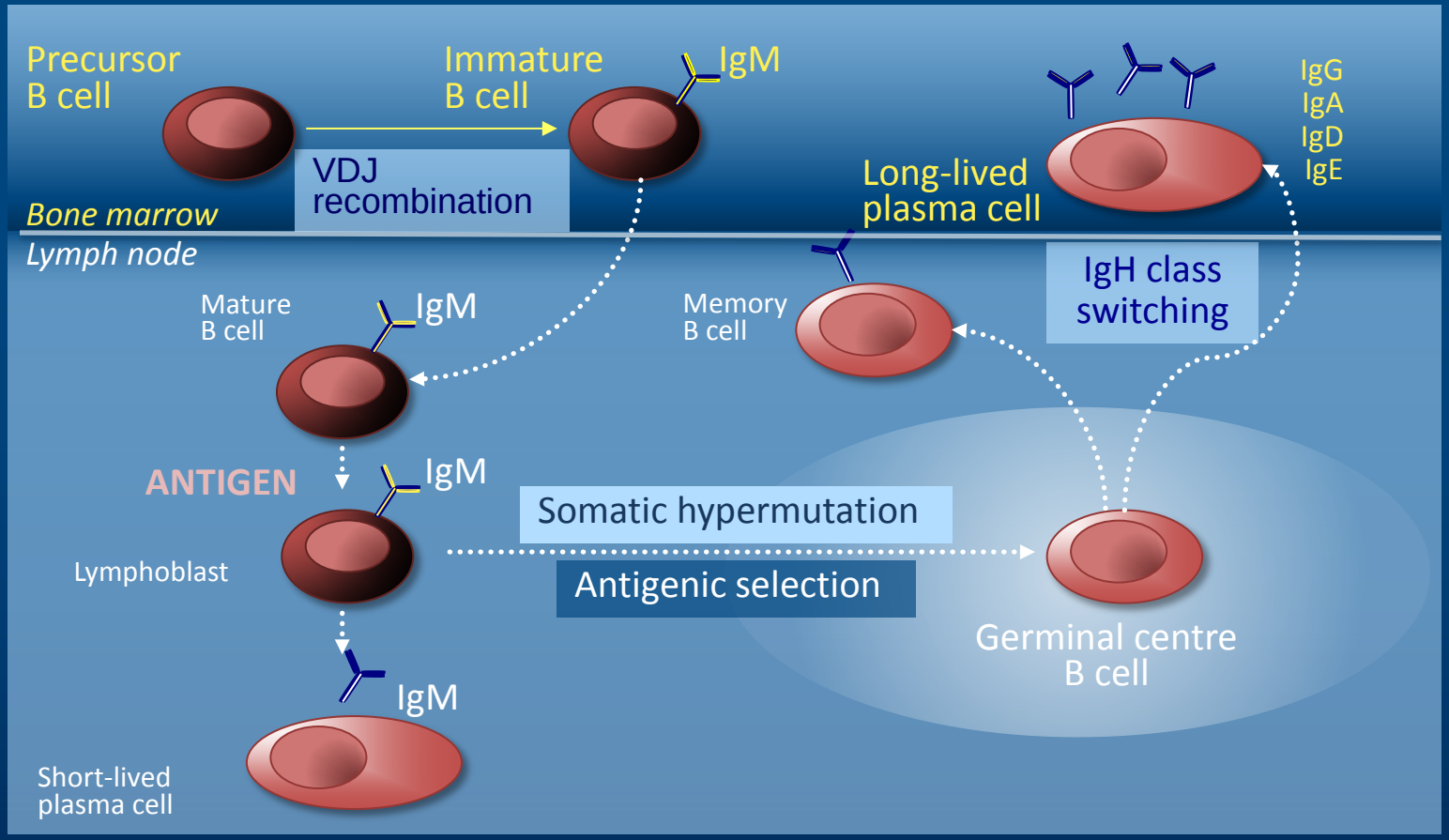
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
National Comprehensive Cancer Network. http://www.nccn.com

Lymphocyte Development



B-lymphocyte to Plasma Cell

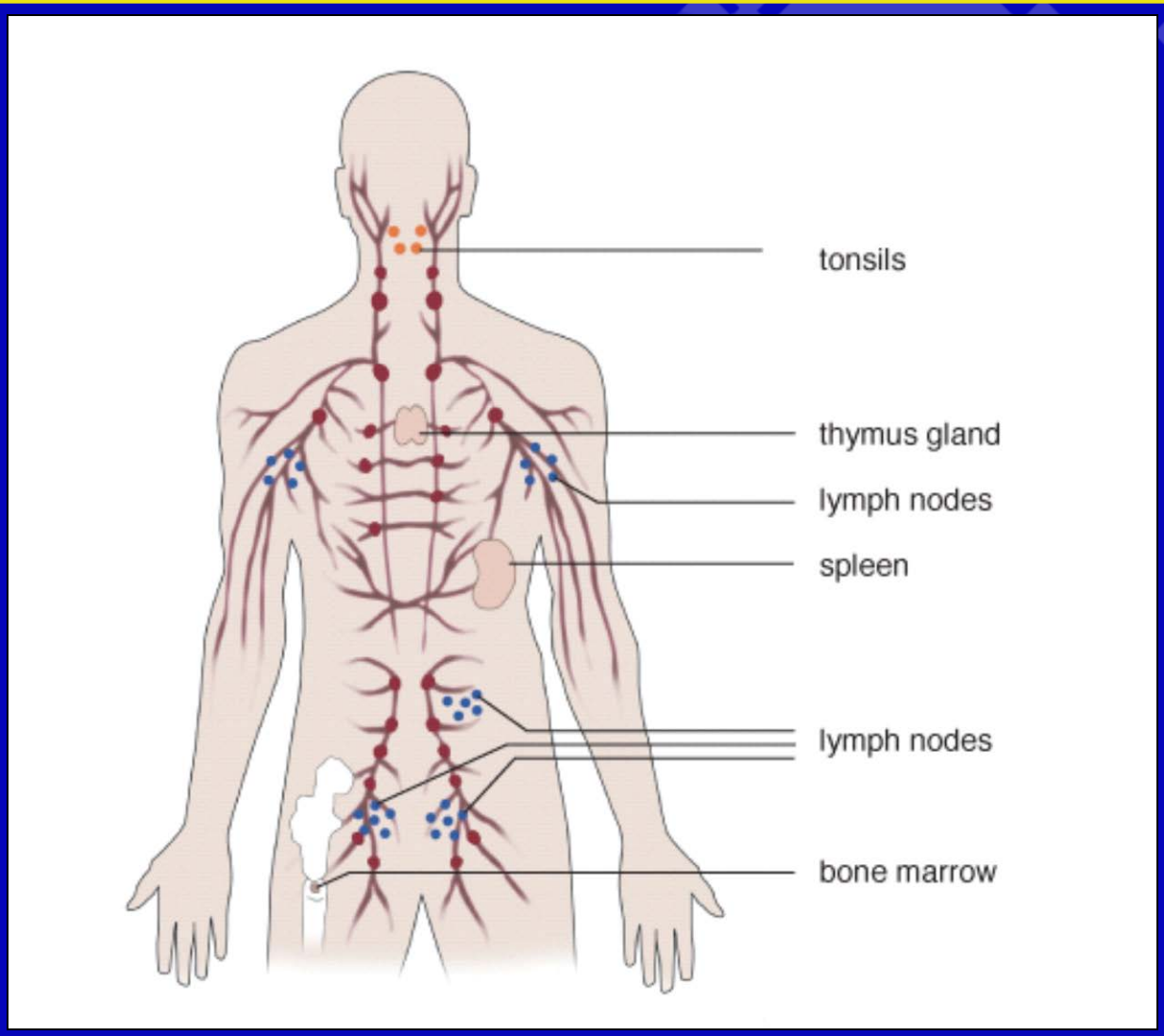
The process of immature B cells becoming plasma cells is associated with genetic instabiliy.[1] Multiple myeloma is characterized by abnormal plasma cell infiltration of the bone marrow,[1] derived from post-germinal-centre B cells.[2]



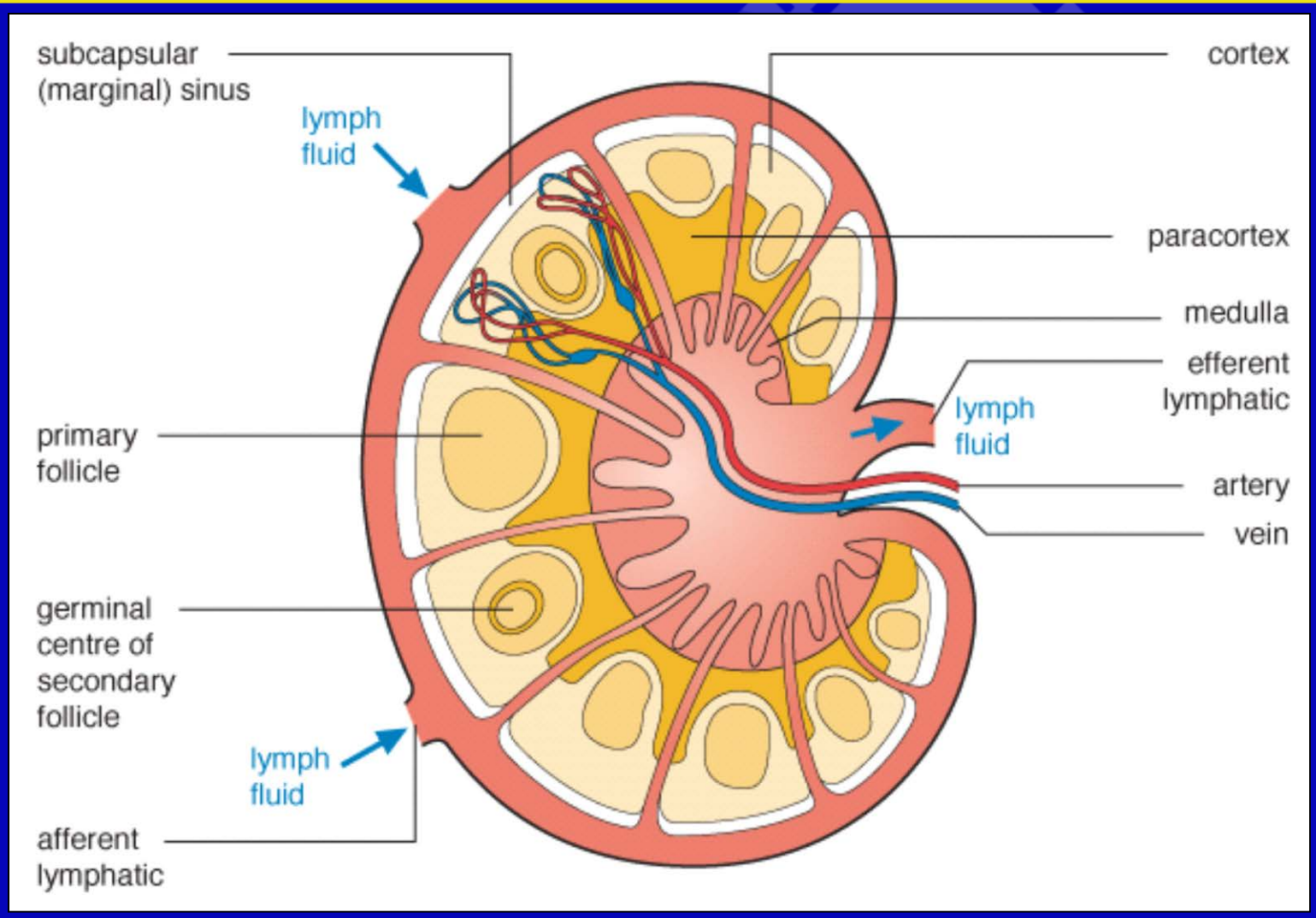
Ig: immunoglobulin; VDJ: variable (diversity) joining.
Adapted from: figure provided by Dr. N Bahlis.

1. Morgan et al. Nat Rev Cancer. 2012;12:335-48; 2. Palumbo and Anderson. N Engl J Med. 2011;364:1046-60.

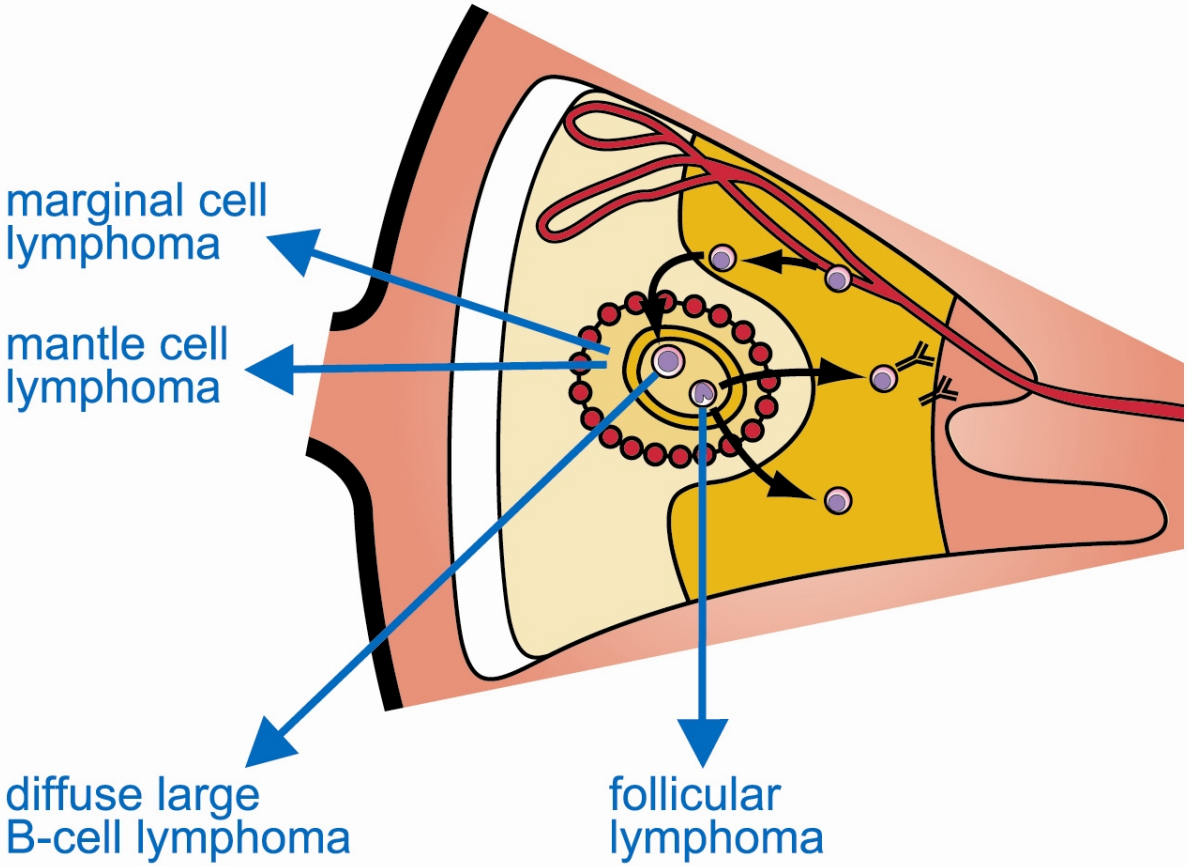
The Lymphatic System



Lymph Node


subcapsular
(marginal) sinus
lymph
fluid
cortex
paracortex
medulla
efferent
lymphatic
lymph
fluid
primary
follicle
artery
vein
germinal
centre of
secondary
follicle
lymph
fluid
afferent
lymphatic

Natural History *(cont'd)*



Estimates for Cancer Incidence and Mortality in Canada, 2010

- An estimated 173,800 new cases of cancer and 76,200 deaths from cancer will occur in 2010
- An estimated 7,500 new cases of NHL will develop in 2010
- NHL is the fifth most common cancer and the incidence is increasing

Canadian Cancer Society. http://www.cancer.ca
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.

Risk Factors

- Genetic abnormalities
- Viral infections
- Immune disturbances
- Primary immune deficiency diseases and acquired immunosuppression
- Many patients with NHL have no risk factors

Hennessy BT, *et al*. *Lancet Oncol* 2004;5:341-53.
Zinzani PL. *Semin Oncol* 2005;32(Suppl 1):S4-S10.
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
Multani P, *et al*. *Curr Pharma Biotechnol* 2001;279-91.

Signs and Symptoms

- Wide range of signs and symptoms
  - a. Enlarged lymph nodes
  - b. Fever
  - c. Night sweats
  - d. Weight loss
- “B” symptom designation if any of b, c or d from above

Zinzani PL. *Semin Oncol* 2005;32(Suppl 1):S4-S10.
Armitage JO. *CA Cancer J Clin* 2005;55:368-76.

Signs and Symptoms *(cont'd)*

- Other possible signs and symptoms
- Presence of these signs is dependent on the site and extent of the disease
- Symptoms may include:
  - Abdominal discomfort (pain, bloating, increased girth)
  - Non-specific flu-like symptoms
  - Fatigue, low energy
  - Back pain
  - Gastrointestinal complaints
  - Itchiness
  - Cough, dyspnea and chest pain occur in 20% of patients

The Leukemia and Lymphoma Society. http://www.leukemia-lymphoma.org
Arimura K, *et al*. *Haematologica* 2003;88:ECR34.

Non-Hodgkin's Lymphoma

Diagnosis and Classification of Non-Hodgkin's Lymphoma

Diagnostic and Investigative Techniques

Test	Examples
Blood Tests	Hematology (complete blood count, blood chemistry and erythrocyte sedimentation rate)
Imaging	X-rays, gallium scans, ultrasound, MRI, PET scans
Biopsy/Cytology	Suspicious lymph node, bone marrow
Molecular Analysis	Morphology, immunophenotyping, immunohistochemistry, flow cytometry, genotype testing

Biopsy/Cytology

- Types of tissue sampling include:
  - Incisional or excisional biopsy
  - Core needle biopsy
  - Fine needle aspirate

Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
Canadian Cancer Society. http://www.cancer.ca/ccs/internet/standard/0,3182,3172_10175_254247_langId-en,00.html
Rhode Island Cancer Council. http://www.ricancercouncil.org
Gong JZ, *et al*. *Diagn Cytopathol* 2004;31:23-30.
Hehn ST, *et al*. *J Clin Oncol* 2004;22:3046-52.

Classification Systems

- Numerous classification systems have developed over the years
  - International Working Formulation (IWF)
  - Revised European-American Classification of Lymphoid Neoplasms (REAL)
  - World Health Organization (WHO) classification system (is now the currently accepted system)

International Working Formulation (IWF)

- Published in 1982 by the National Cancer Institute
- Single, unified classification system
- Divides lymphomas into low, intermediate and high-grade
- Low grade = slow-growing
- High grade = rapidly progressing

National Cancer Institute. *Cancer* 1982;49:2112-35.

WHO Classification

- Developed in 1999
- Updated version of the REAL classification
- Accepted worldwide
- Recently updated in 2008
  - American (SH) and European (EAHP) hematopathology societies
  - ~ 75 authors: US, Canada, Europe, Asia, Australia
  - WHO Clinical Advisory Committees
    - ~ 100 international hematologists and oncologists
    - Consensus meeting: Lyon, Sept. 2007

WHO Classification

B-cell

Indolent
- Small lymphocytic / CLL
- Lymphoplasmacytic
- Follicular, any type
- Marginal zone
  - MALT (mucosa-associated)
  - nodal
  - splenic

Aggressive
- Diffuse large cell, any type
- Mantle cell
- Burkitt-like

Leukemia-like
- Lymphoblastic
- Burkitt

Viral
- Primary effusion lymphoma (HHV-8)

T-cell / NK-cell

Indolent
- Mycosis fungoides
- T-cell granular lymphocytic
- Anaplastic large cell, cutaneous

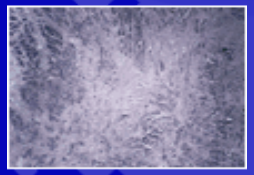
Aggressive
- Peripheral T-cell, not otherwise characterized
- Angioimmunoblastic
- Anaplastic large cell, systemic
- NK / T-cell nasal and nasal-type
- Enteropathy associated
- Hepatosplenic $\gamma\delta$
- Subcutaneous panniculitis-like

Leukemia-like
- Lymphoblastic
- T-cell prolymphocytic
- NK-cell leukemia

Viral
- Adult T-cell lymphoma / leukemia (HTLV-1 +)

Molecular Analysis

- Morphology
- Immunophenotyping
- Immunohistochemistry
- Flow cytometry
- Genotype testing

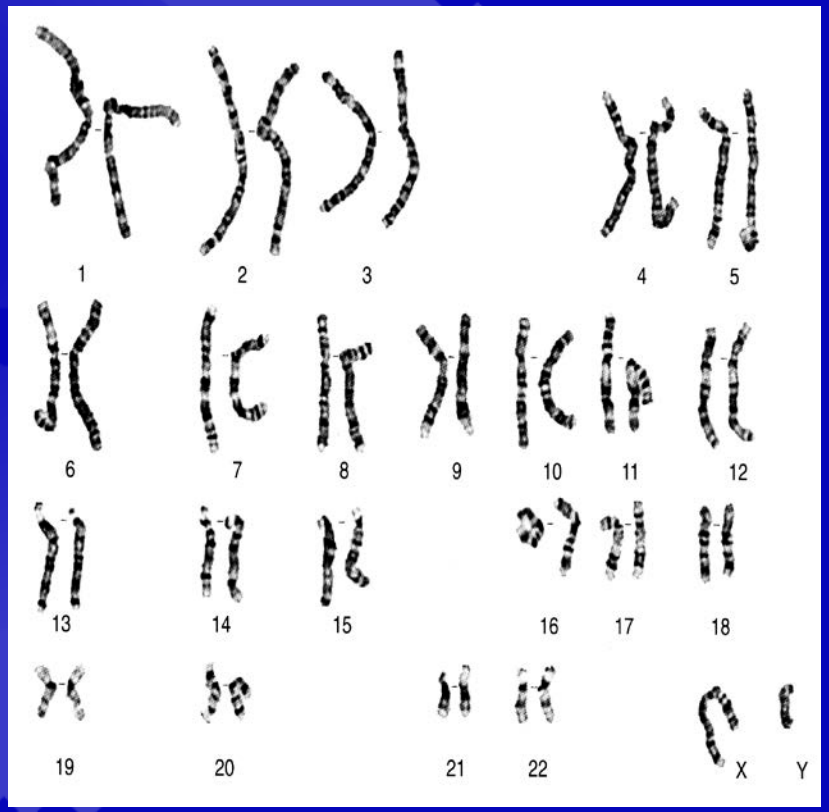


Zinzani PL. *Semin Oncol* 2005;32(Suppl 1):S4-S10.

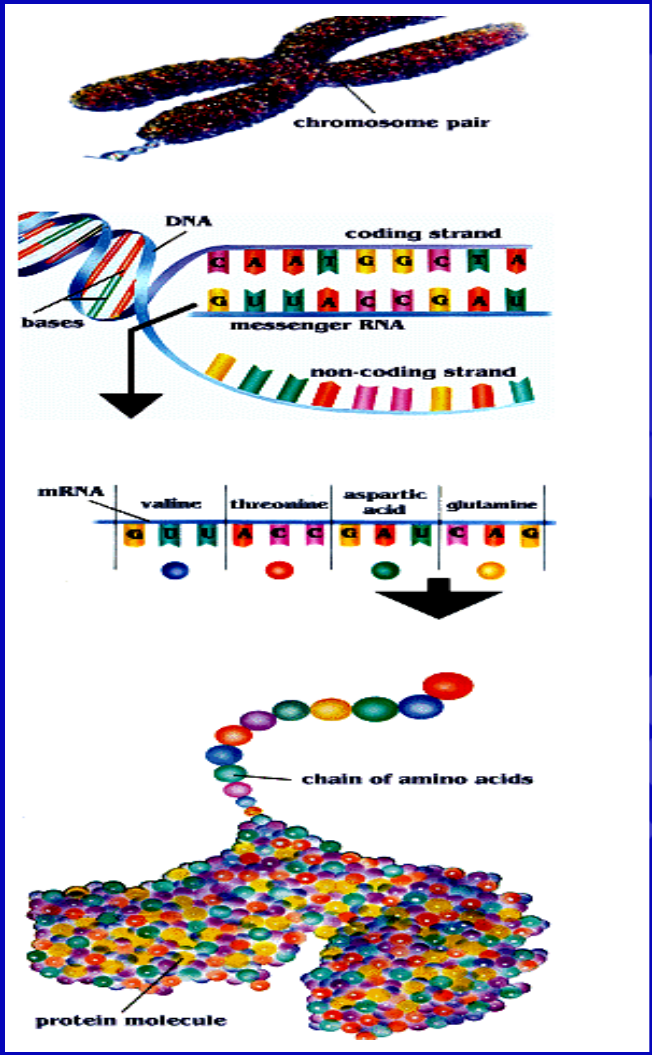
Human Chromosomes

Human cells have 46 chromosomes

- **23 pairs of chromosomes**
- **one of each of the 23 pairs comes from each parent at conception**
- **each chromosome contains DNA and carries many 1000s of genes**



Molecular Biology:

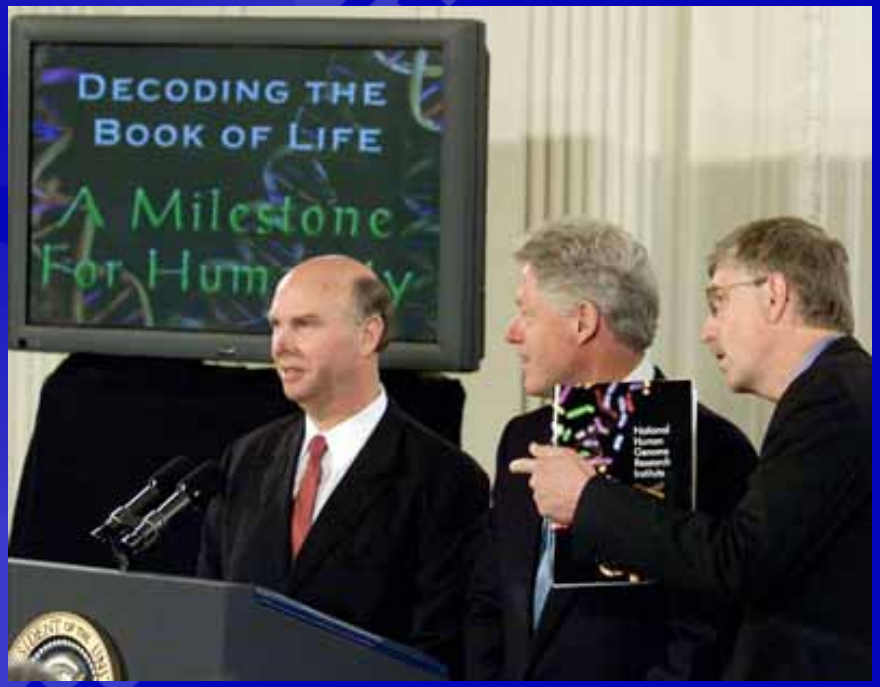


DNA makes….

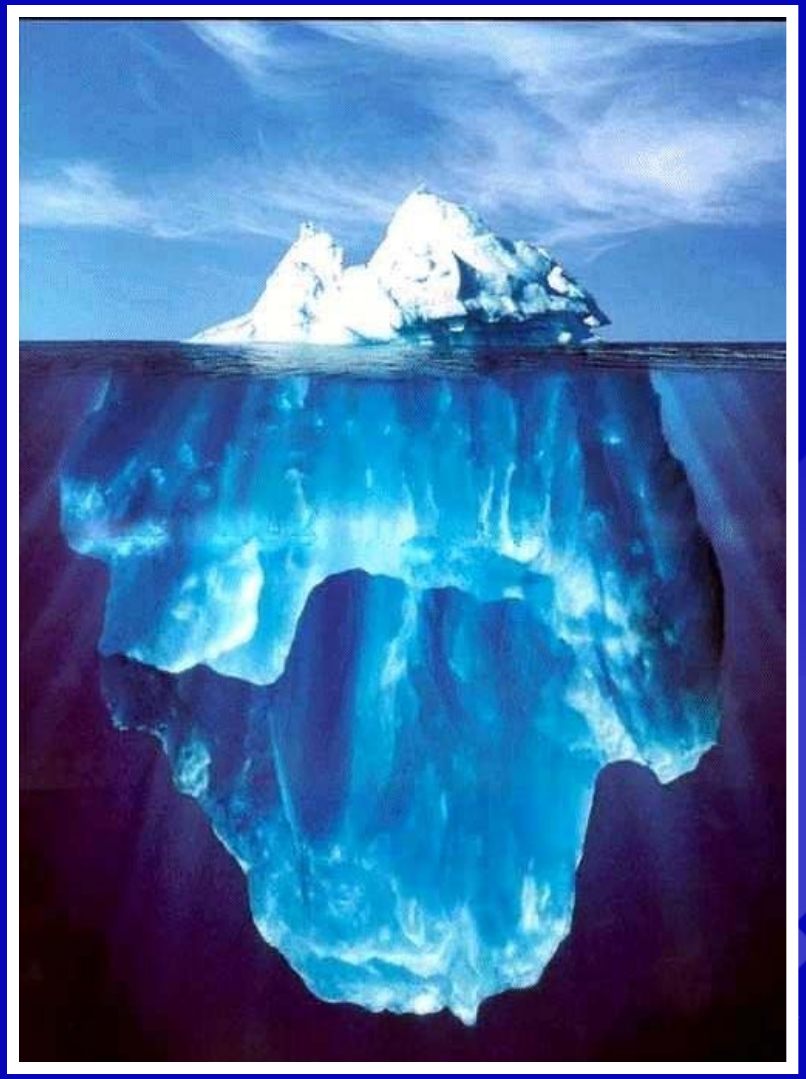
RNA makes….

protein

The Human Genome



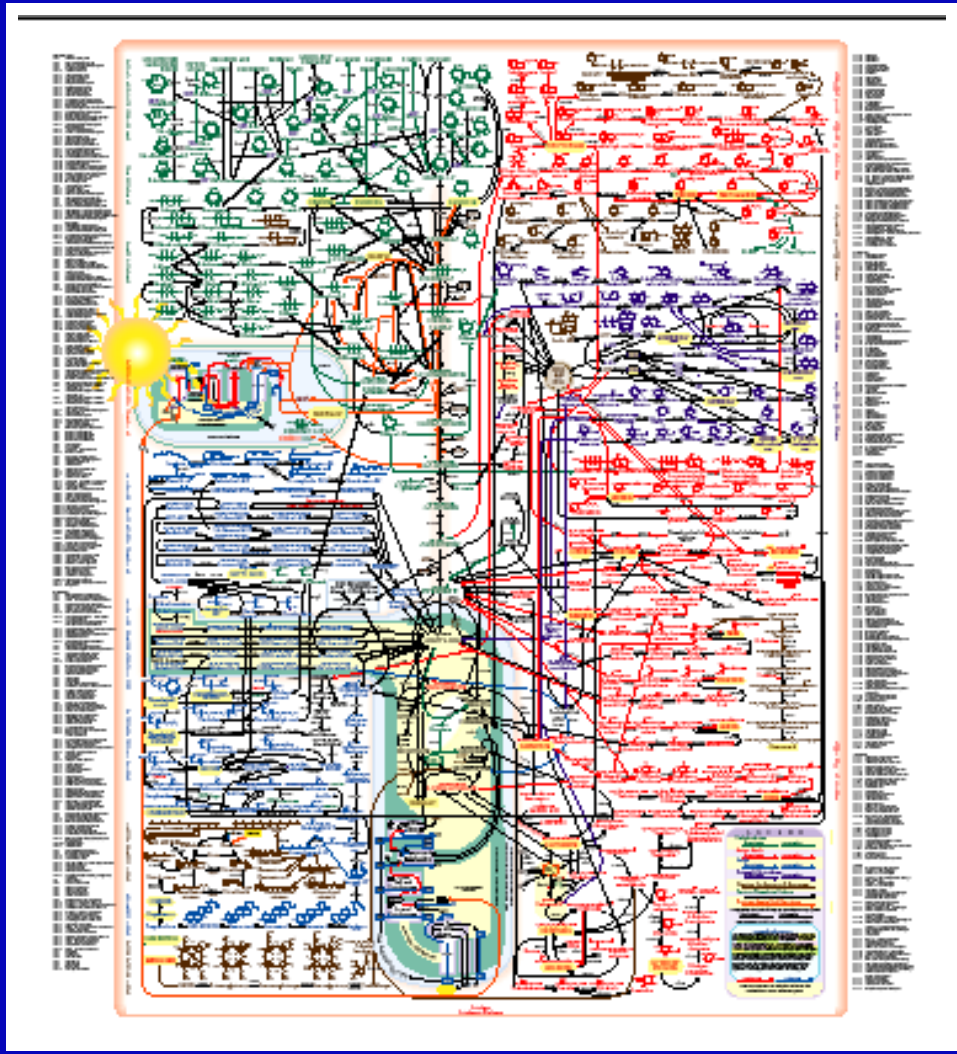
The tip of the iceberg…



Diseases for which we have a gene.

Diseases for which we don’t..

Complexity of Biological Pathways

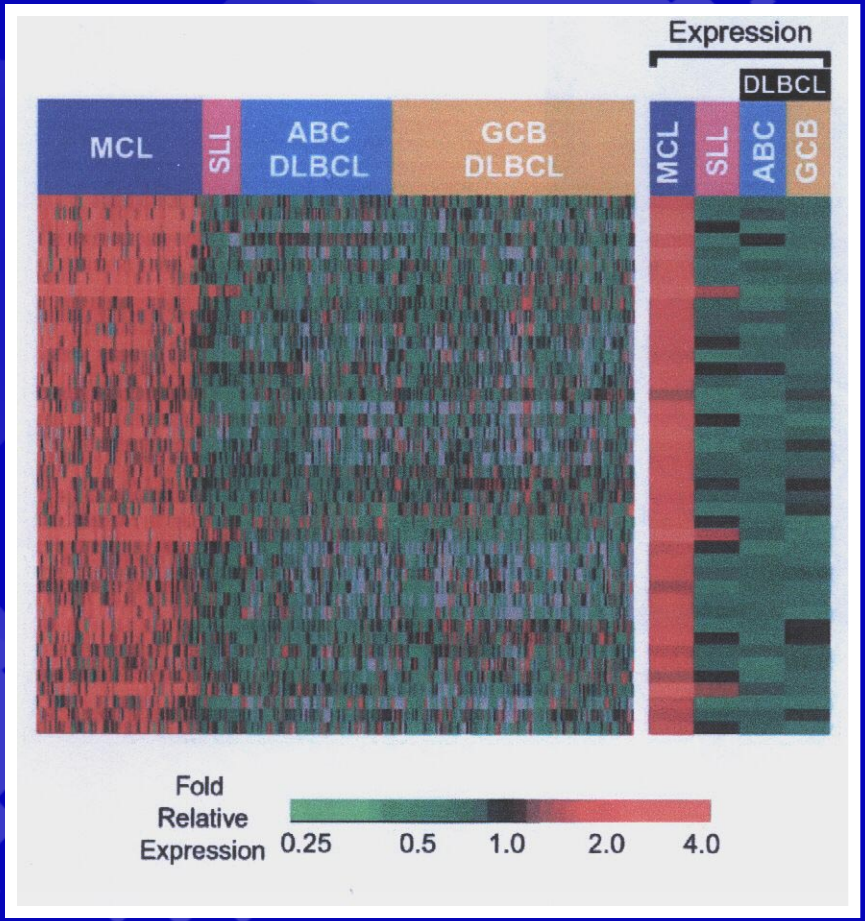


- ✓ Genes don't work alone
- ✓Every gene product interacts with multiple other gene products, and with the environment

Molecular Diagnosis of MCL

Several thousand genes differentially expressed in MCL vs. other lymphoma subtypes →

42 'MCL signature genes'



(Rosenwald et al. 2003. *Cancer Cell*. 3:185)

Oncogenes in NHL

Oncogenes linked to NHL in ≥ 50% of cases

Gene	Lymphoma	Translocation	Gene Product	Frequency
Bcl-1	Mantle cell	11;14	Cyclin D1	95
Bcl-2	Follicular	14;18	Anti-apoptosis	85
Myc	Burkitt's	8;14	Cell cycle upregulator	95
ALK	Anaplastic large cell	2;5	?	60
PAX-5	Lymphoplasmacytic	9;14	B cell activator	50

System Configuration

The HeliScope
- Laser Illumination
- CCD Camera
- Microfluidics
- High-speed stage
- Instrument-control computer

Data Transfer to bioinformatics tower does not impact run time of HeliScope

Image-processing computer tower

For Sequencing
Designed to align a 10X human genome sequence data set in ~24 hours.

For Gene Expression
Designed to process tens of thousands of samples in ~24 hours.

Alignment/ Bioinformatics tower

Non-Hodgkin's Lymphoma

Prognostics

Prognostic Markers

- Molecular (biologic) markers
- Clinical markers
- Prognostic models
  - International Prognostic Index (IPI) (for all types of lymphomas)
  - Follicular Lymphoma International Prognostic Index (FLIPI) (for follicular lymphoma only)

IPI

- IPI evaluates five variables:
  - Age >60 years
  - Advanced Stage III/IV
  - Performance status >2
  - Number of extranodal sites involved >1
  - Serum LDH > Normal

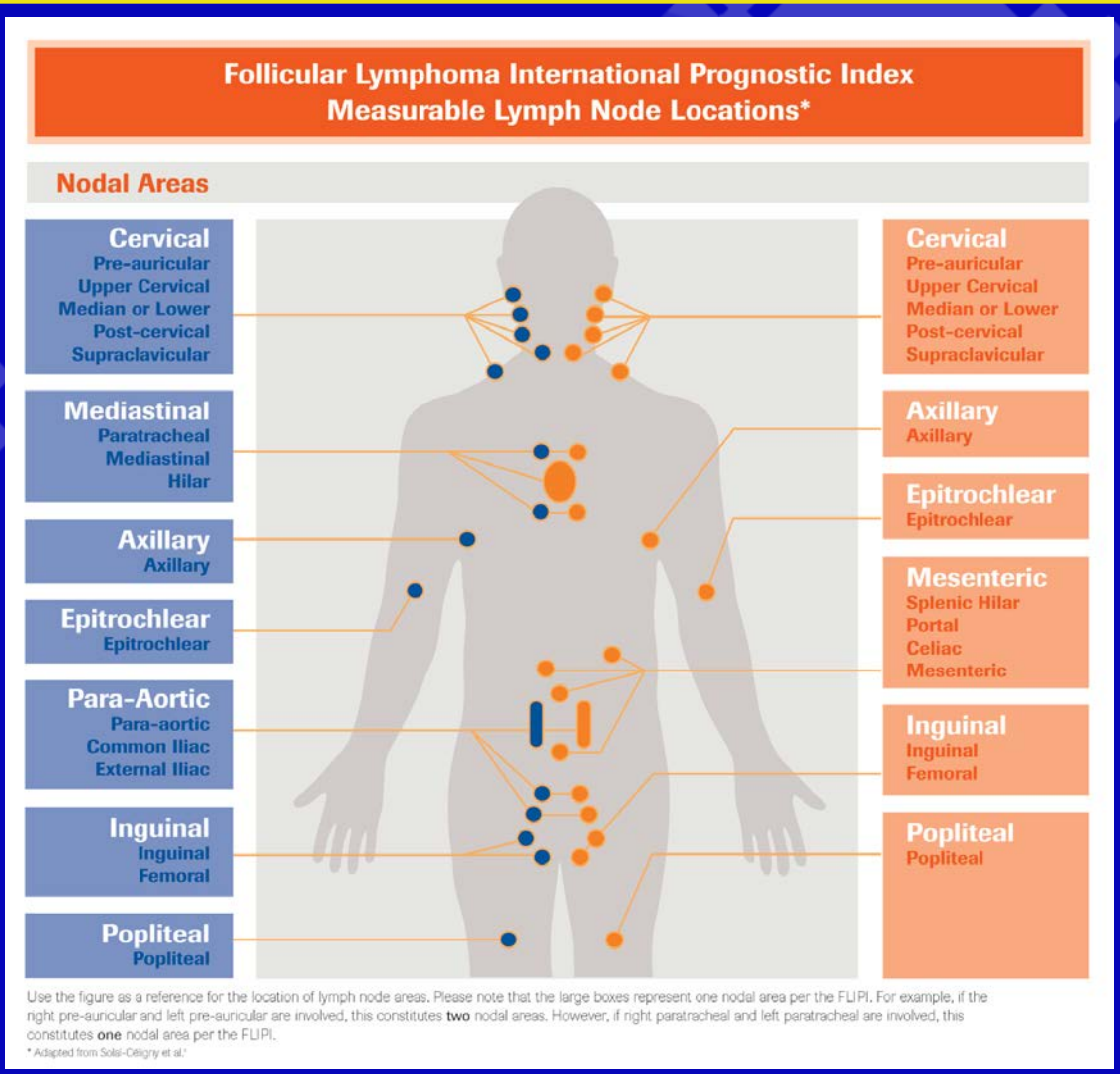
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
Armitage JO. *CA Cancer J Clin* 2005;55:368-76.
N Eng J Med 1993;329:987-994.

FLIPI

- FLIPI evaluates five variables:
  - Age >60 years
  - Baseline hemoglobin <120 g/L
  - Serum LDH >Normal
  - Advanced Stage III or IV
  - Number of nodal sites >4
- Defines three risk groups, scores ranging from 0 to 5

Solal-Celigny P, *et al*. *Blood* 2004;104:1258-65.
Long J, *et al*. *Semin Oncol Nurs* 2006;22:97-106.

FLIPI



Solal-Celigny P, et al. *Blood* 2004;104:1258-65.

FLIPI *(cont'd)*

- **Risk groups:**
  - **Good prognostic group (score = 0-1)**
  - **Intermediate prognostic group (score = 2)**
  - **Poor prognostic group (score = 3+)**

Solal-Celigny P, *et al*. *Blood* 2004;104:1258-65.

Non-Hodgkin's Lymphoma

Staging

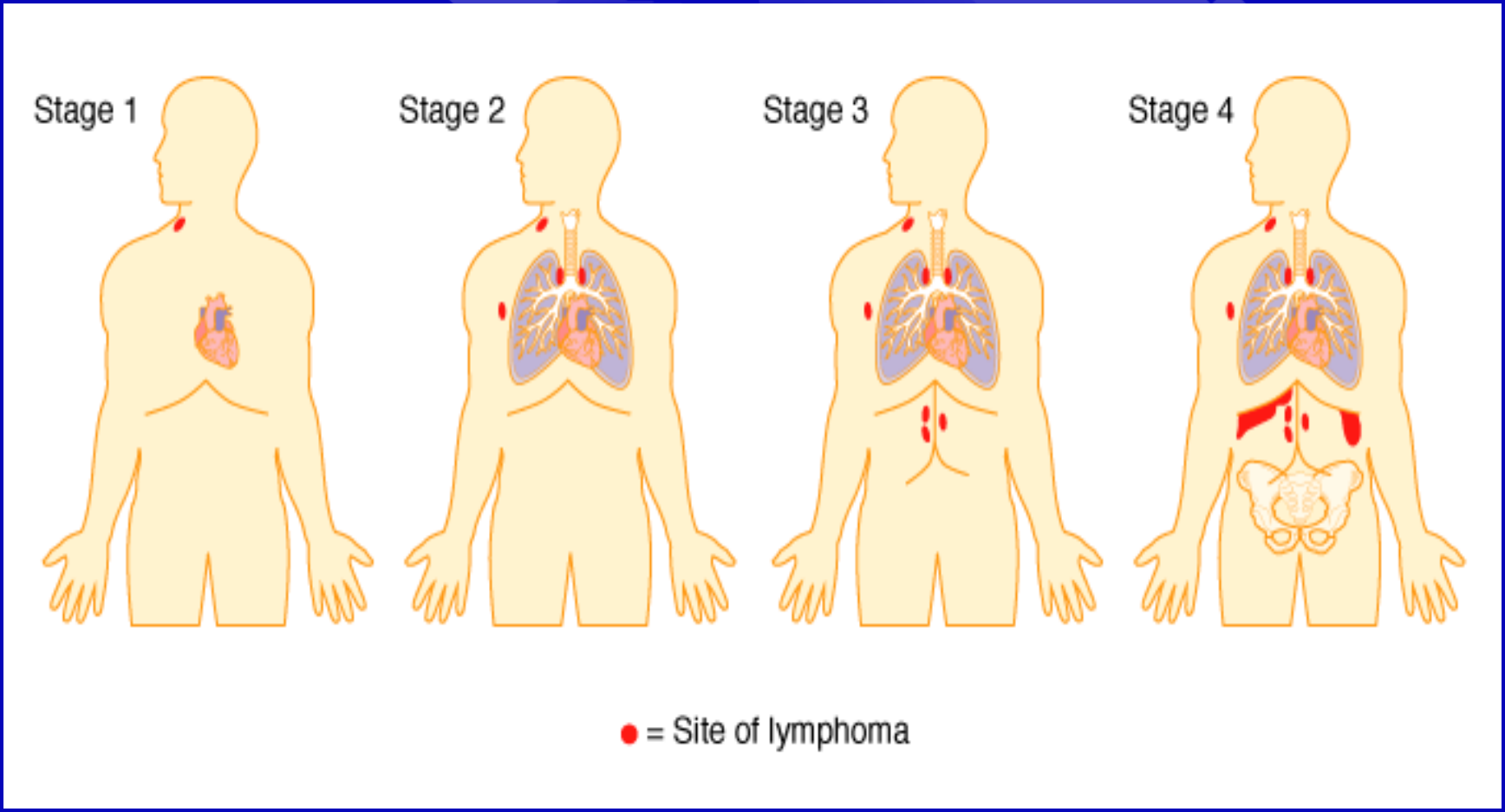
Staging Disease

- Comprises comprehensive diagnostic work-up to determine:
  - Extent of the disease
  - Bulk of tumour mass
  - Potential for complications
  - Type of treatment required

Staging Disease *(cont'd)*

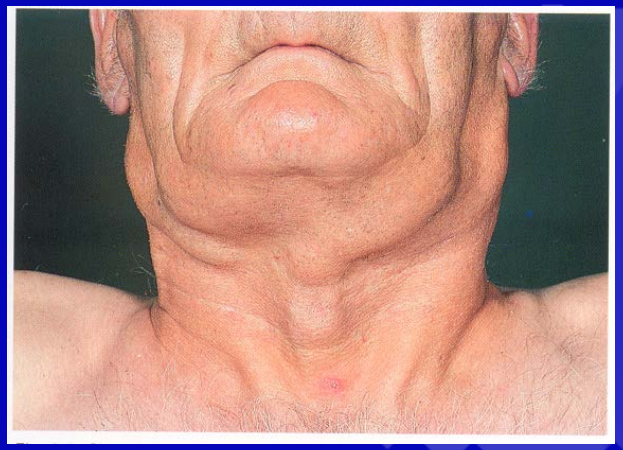
- **Baseline staging may include:**
  - **Pathology review**
  - **History and physical examination**
  - **Blood work**
  - **Chest x-ray**
  - **CT scan**
  - **Bone marrow biopsy and aspiration**
  - **Gallium scan**
  - **Lumbar puncture**
  - **Cardiac work-up**

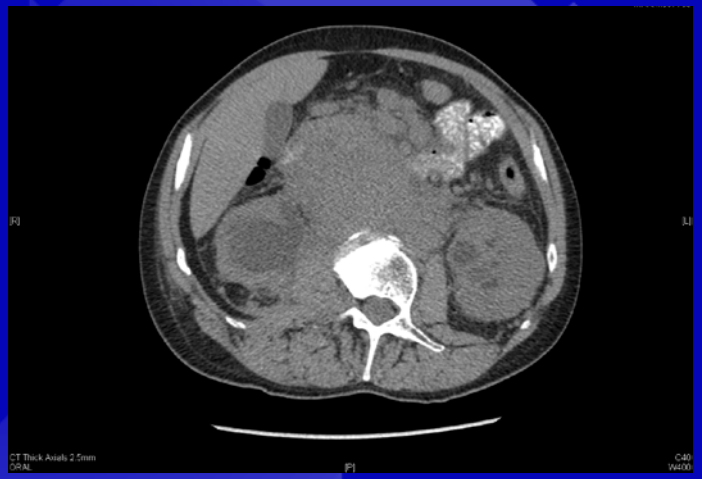
Ann Arbor Staging System *(cont'd)*

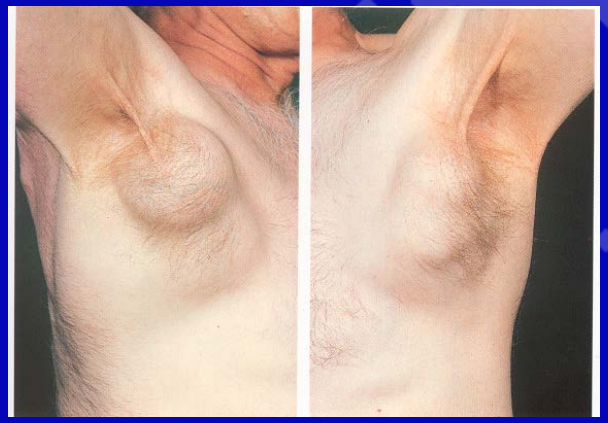


Non-Hodgkin's Lymphoma: A Meeting Resource for Nurses. Hoffmann-La Roche Limited.

Staging Disease *(cont'd)*



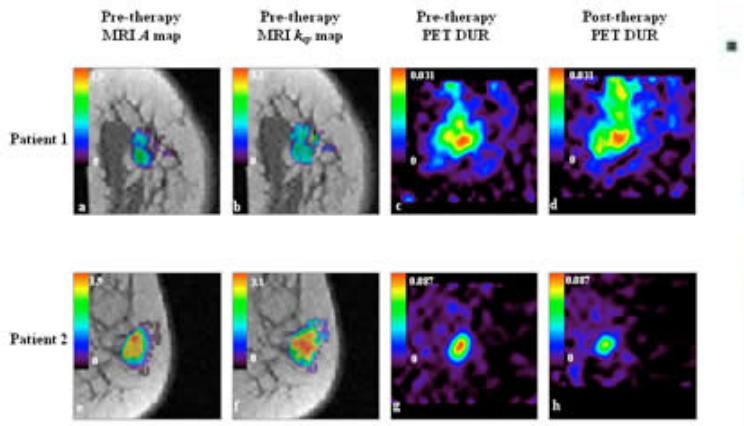




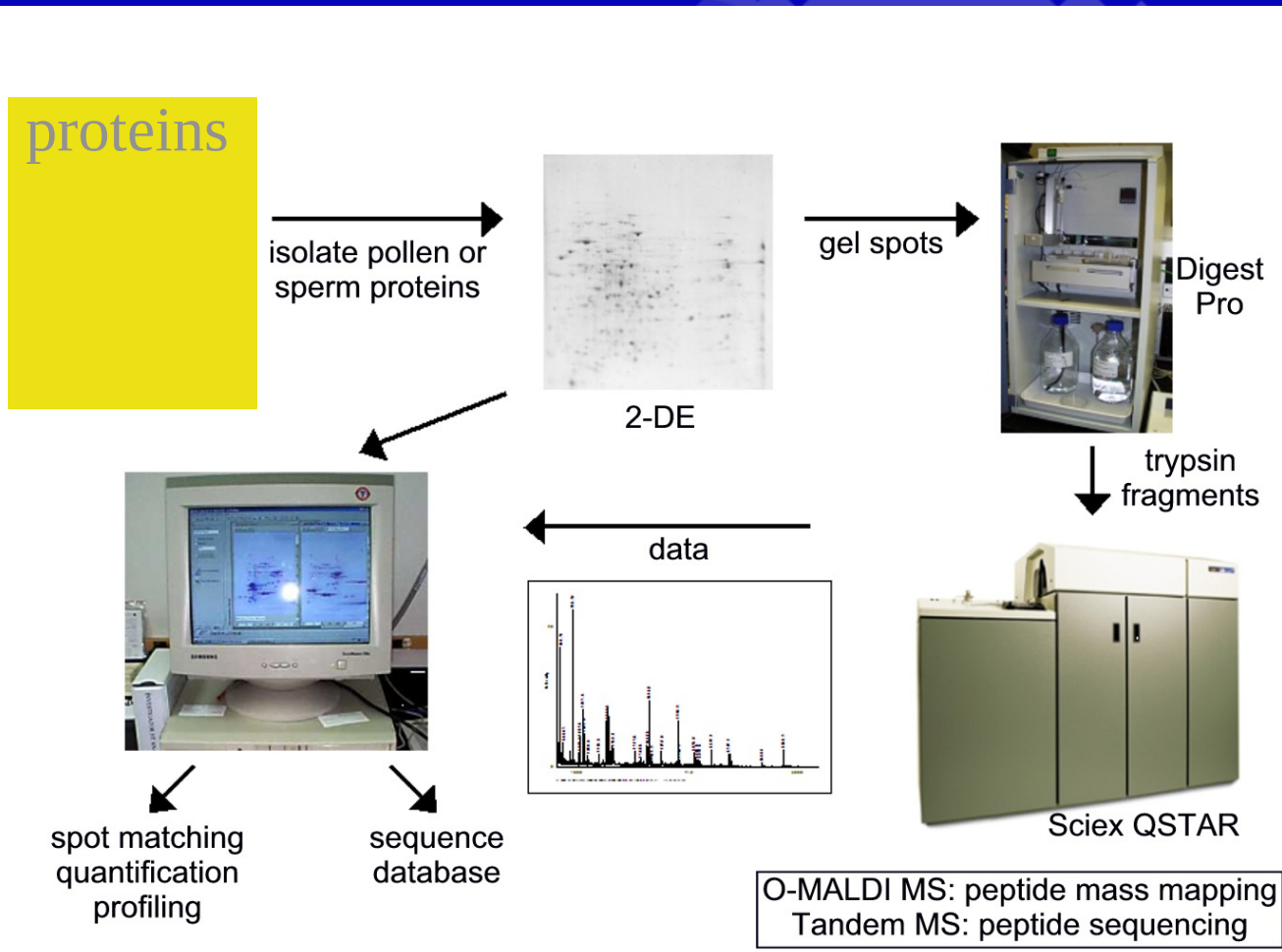
Can we do a better job of finding a cancer at an early stage!!!

One Millimeter Challenge

Lets see cancers less than a millimiter



Can we find early cancers with blood tests



Non-Hodgkin's Lymphoma

Treatment

Natural History

- NHLs are either indolent or aggressive lymphomas
- Classified based on cell behaviour and histology
- Majority of indolent lymphomas are follicular lymphomas that grow slowly and may be widespread at the time of diagnosis

Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
Zinzani PL. *Semin Oncol* 2005;32(Suppl 1):S4-S10.

Natural History *(cont'd)*

- **For indolent lymphomas:**
  - **Disease waxes and wanes in the early stages**
  - **Patients may remain asymptomatic without treatment for a number of years**
  - **Disease is initially chemo- and radiosensitive but usually relapses and eventually becomes resistant**
  - **Median survival approaches 10 years**

Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.
Zinzani PL. *Leuk Lymphoma* 2003;44(Suppl 4):S6-S14.

Natural History *(cont'd)*

- For aggressive lymphomas:
  - Intermediate and aggressive lymphomas develop and grow more quickly than other subtypes
  - Require immediate treatment
  - Patients may be younger in age
    - Usually symptomatic at time of diagnosis
  - Can be cured in up to ~ 50% of cases

National Marrow Donor Program. http://www.marrow.org
Rogers BB. *Semin Oncol Nurs* 2006;22:67-72.

Overview of Primary Treatment Options

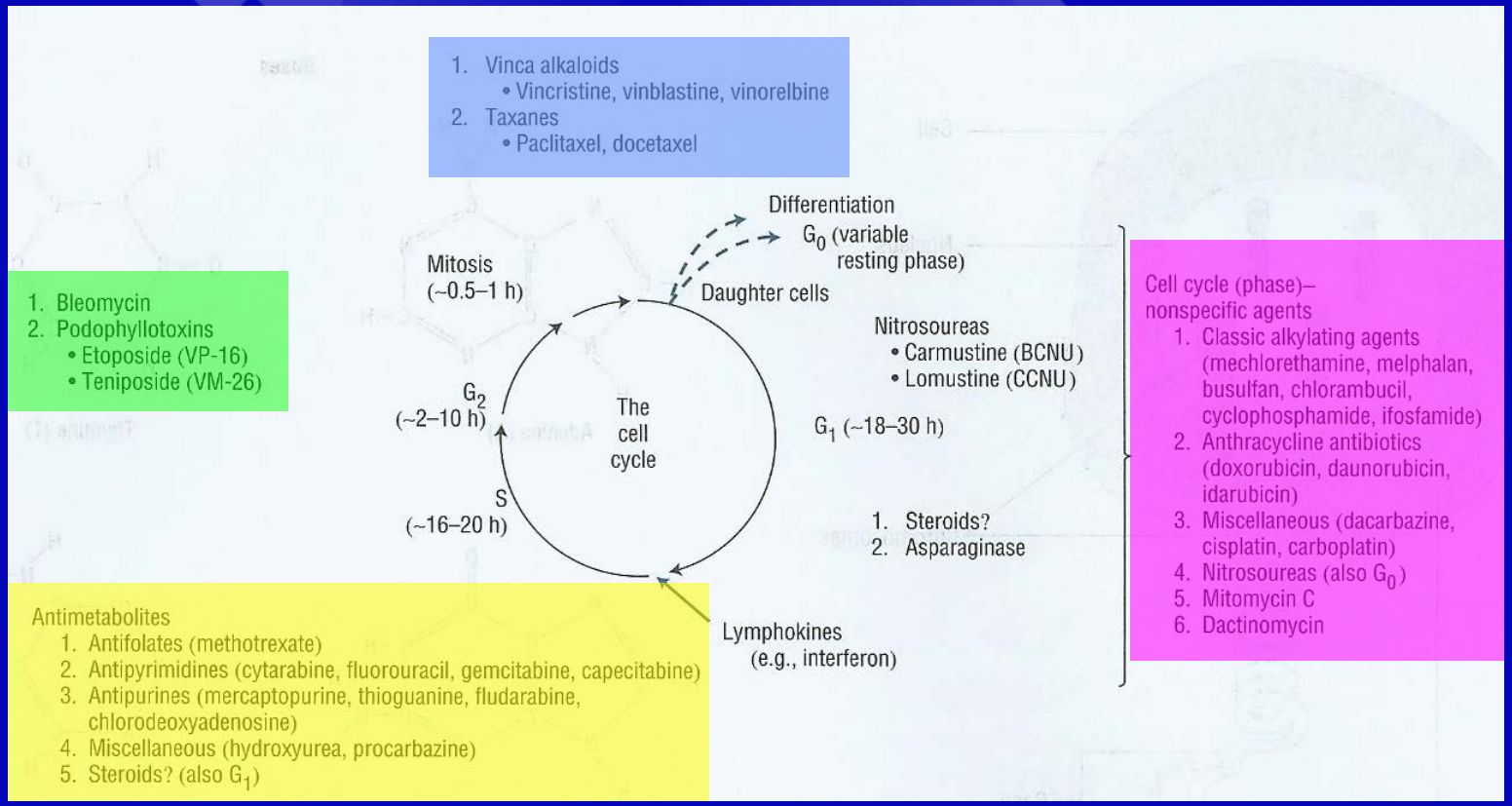
Treatment Option	Description
Watch and Wait	Close monitoring for signs and symptoms of disease progression
Radiation Therapy	Use of high-energy rays to kill lymphoma cells or slow their growth
Chemotherapy	Use of drugs to kill lymphoma cells
Immunotherapy	Use of agents designed to target and destroy lymphoma cells
Transplantation	Infusion of healthy stem cells/bone marrow to help the body restore its supply of healthy blood cells

Chemotherapy

- **Era of modern chemotherapy began in early 1940s**
- Goodman and Gilman **first administered nitrogen mustard to patients with lymphoma**
  - **nitrogen mustard was developed as a war gas rather than as a medicine**
  - **toxic effects on the lymphatic system led to clinical trials**

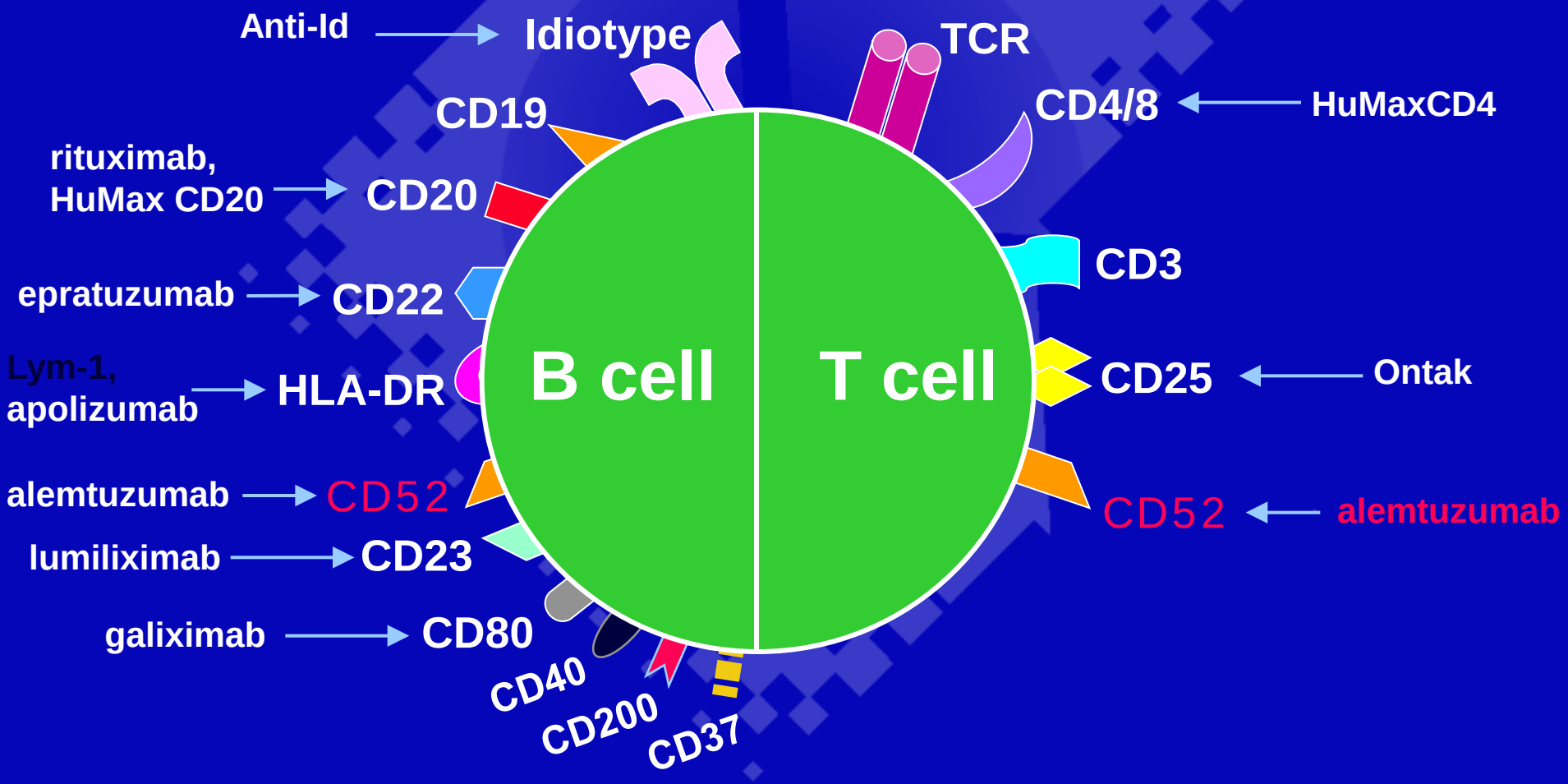
Conventional Chemotherapy

- **Backbone of cancer chemotherapy regimens**
- **Cytotoxicity is not selective**

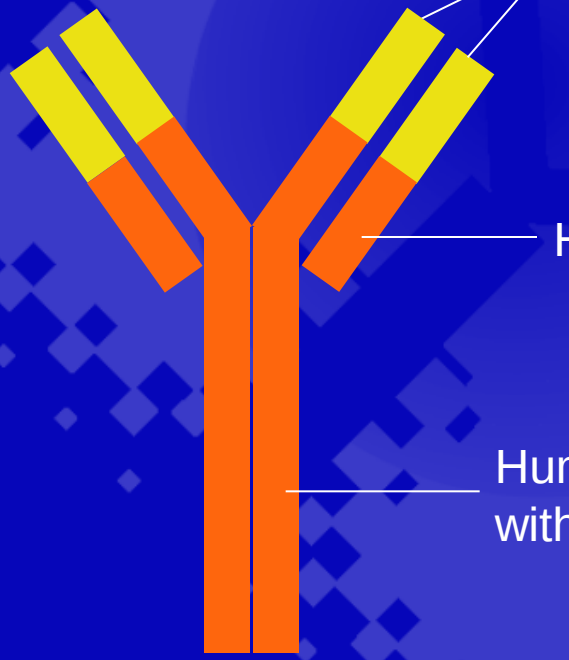


Targeted Therapy – Less Side Effects

Target Antigens in Lymphoid Malignancies



Rituxan®: A Mouse/Human Chimeric MoAb



Murine variable regions bind specifically to CD20 on B cells

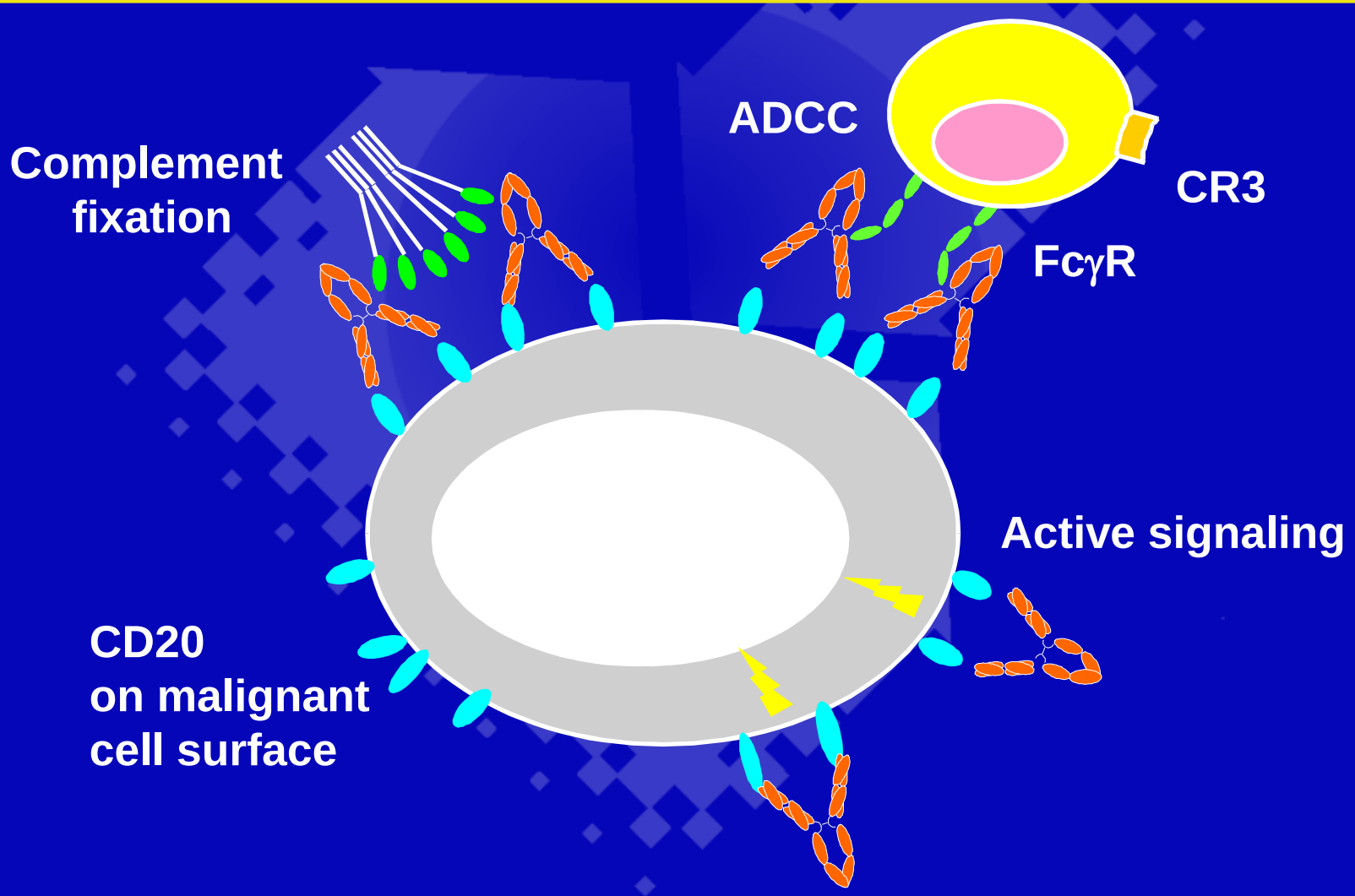
Human kappa constant regions

Human IgG_1 Fc domain works in synergy with human effector mechanisms

Chimeric IgG_1

Rybak et al. *Proc Natl Acad Sci USA.* 1992;89:3165.

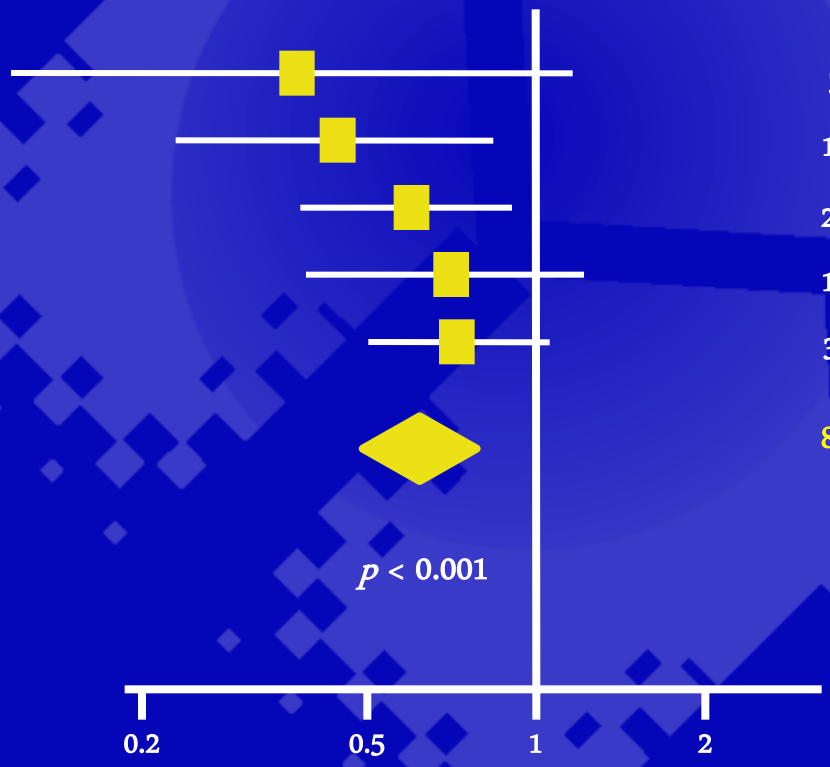
Potential Effects of Anti-CD20 Antibodies on Tumor Cells



Follicular Lymphoma (FL)

Meta-analysis of R-Chemo vs. Chemo in FL

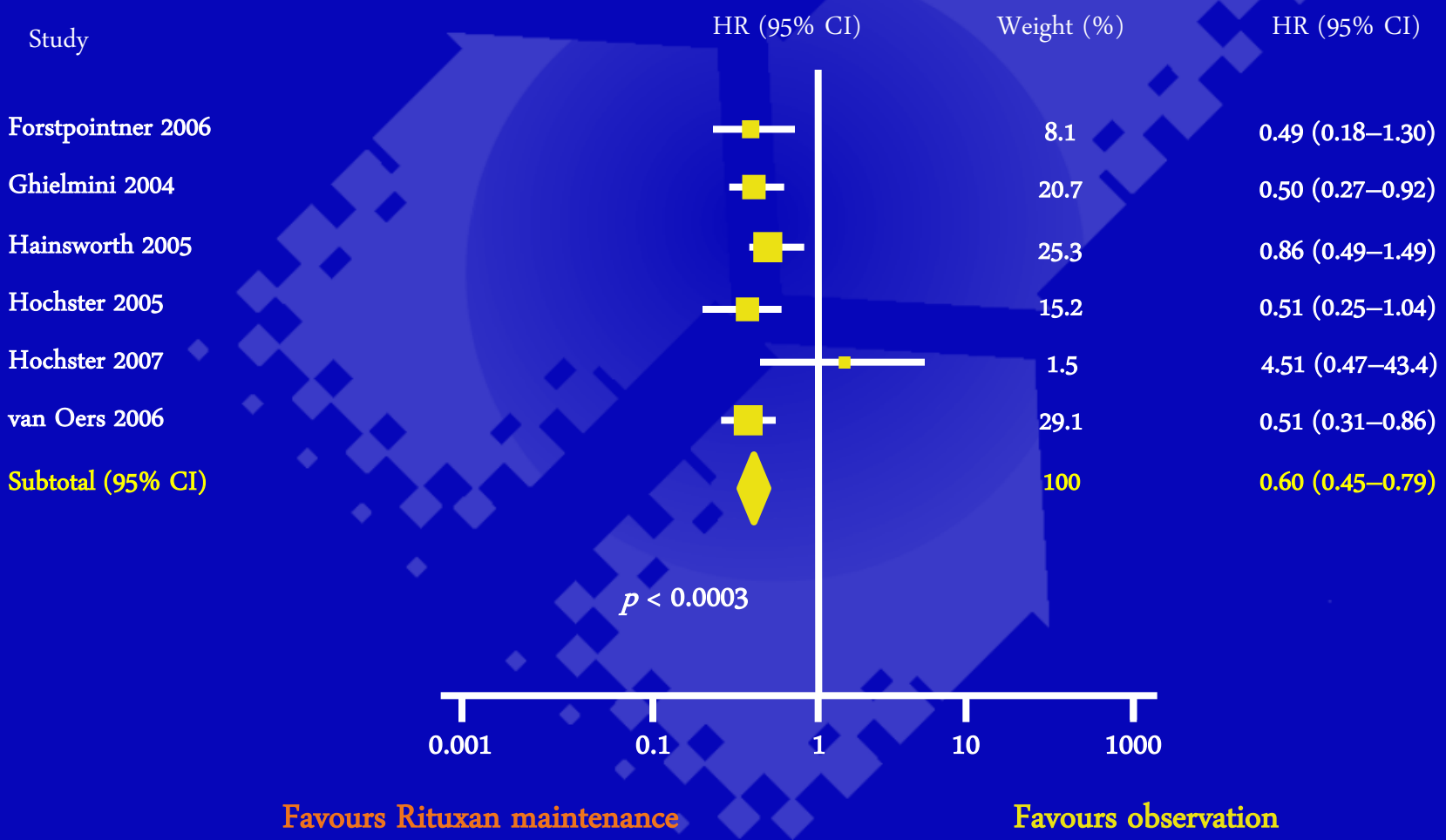
OS benefit demonstrated with rituximab-based treatment



Schulz H, *et al.* J Natl Cancer Inst 2007; 99:706–714.

Meta Analysis: Rituximab as Maintenance in FL

R-Maintenance consistently improves OS vs observation

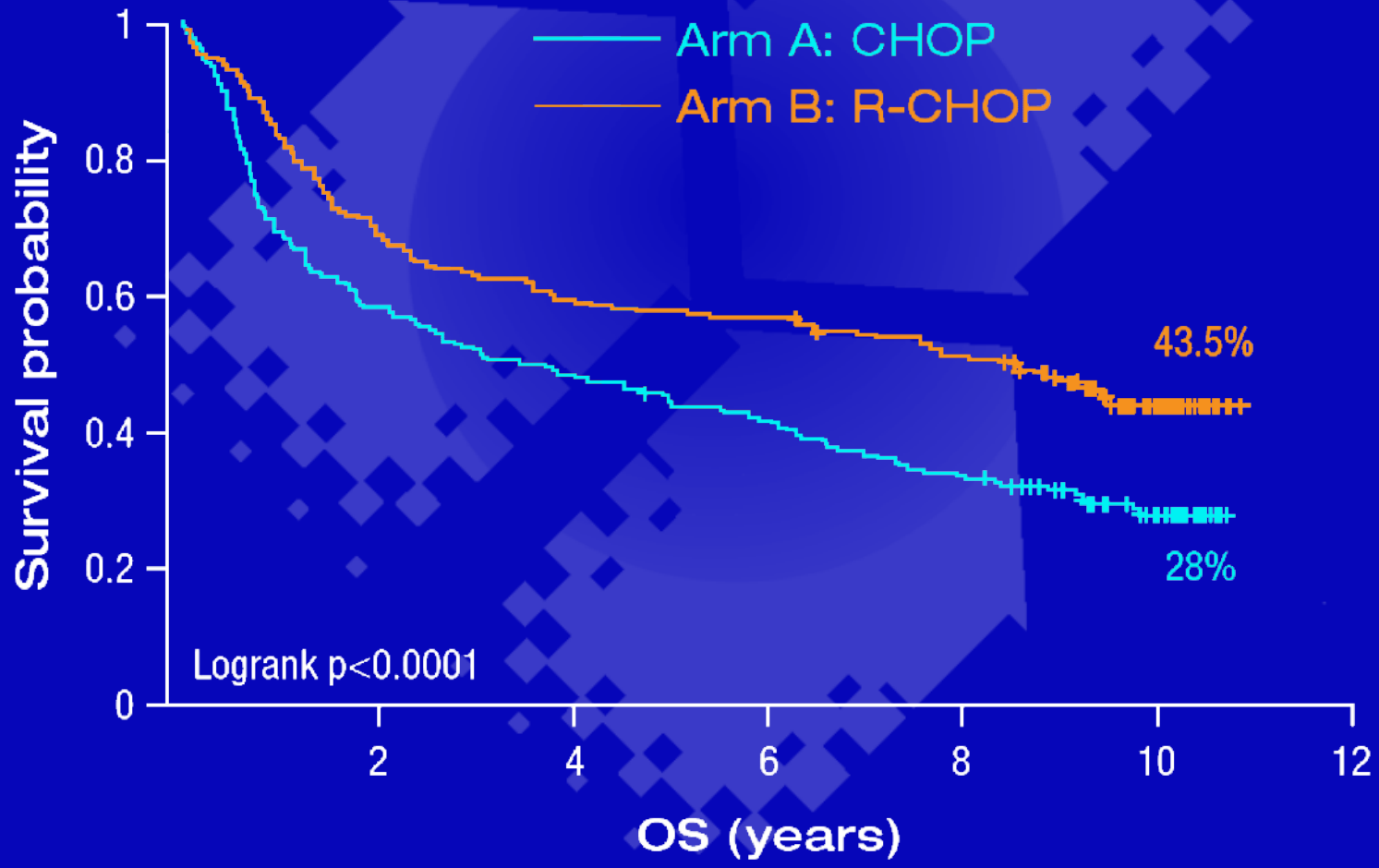


Vidal L, *et al. J Natl Cancer Inst* 2009; 101:248–255.

Diffuse Large B Cell Lymphoma (DLBCL)

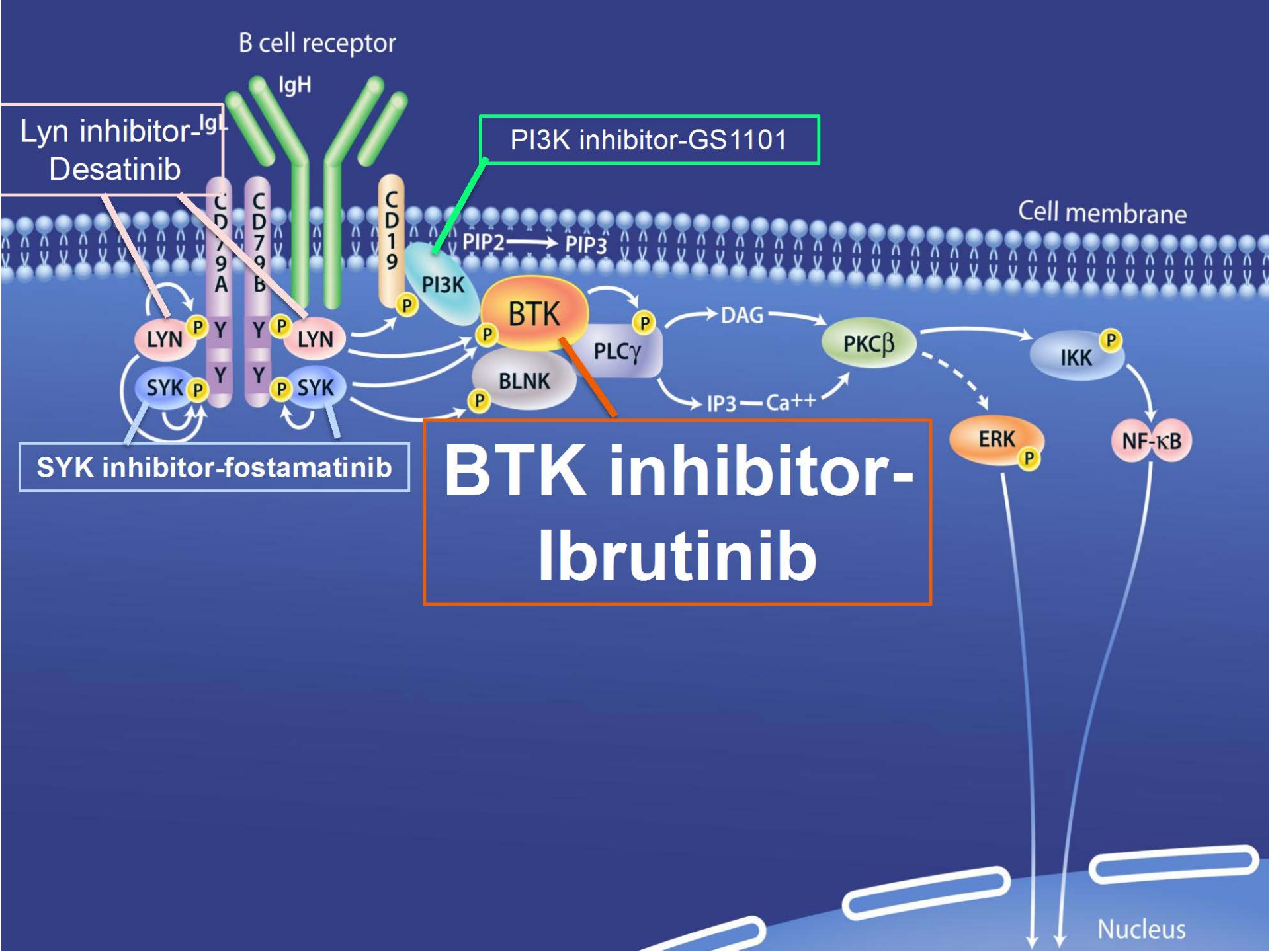
Overall Survival at 10 years

8 cycles of R-CHOP significantly improves OS

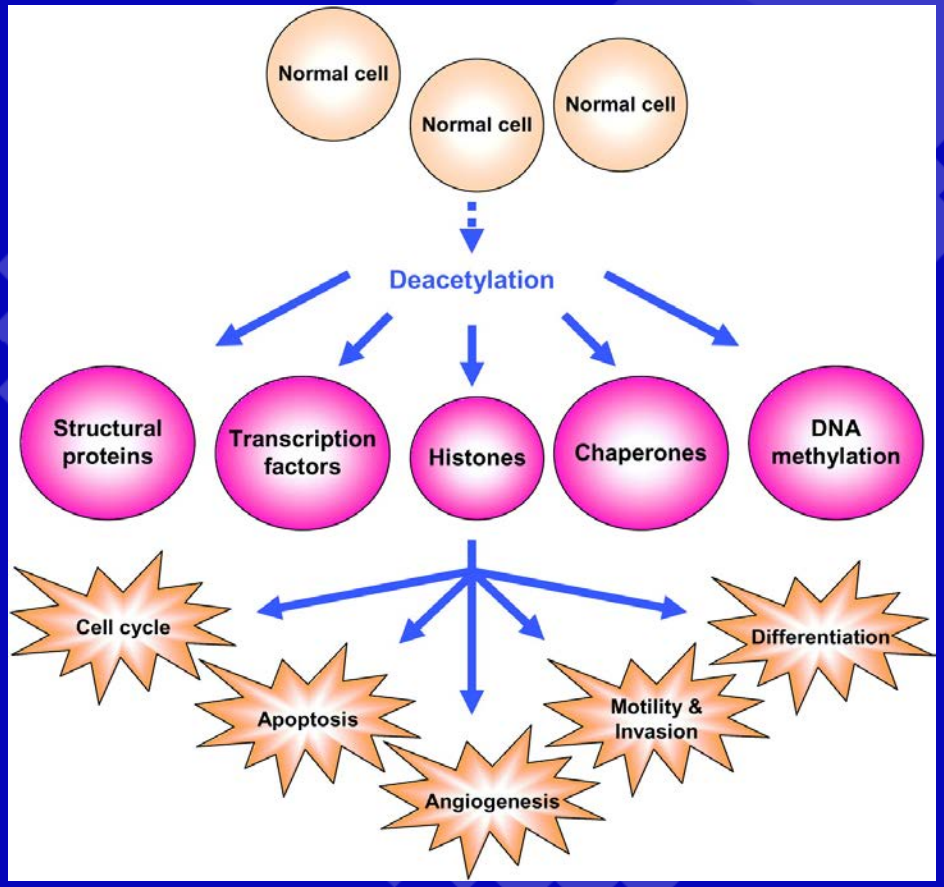


Coiffier B, *et al. Blood* 2010; 116: 2040-2045.

Bendamustine


B cell receptor
IgH
IgL
Lyn inhibitor-Desatinib
PI3K inhibitor-GS1101
Cell membrane
CD79A
CD79B
CD19
PIP2
PIP3
PI3K
BTK
PLCγ
BLNK
LYN
SYK
DAG
IP3
Ca++
PKCβ
IKK
ERK
NF-κB
SYK inhibitor-fostamatinib
BTK inhibitor-Ibrutinib
Nucleus

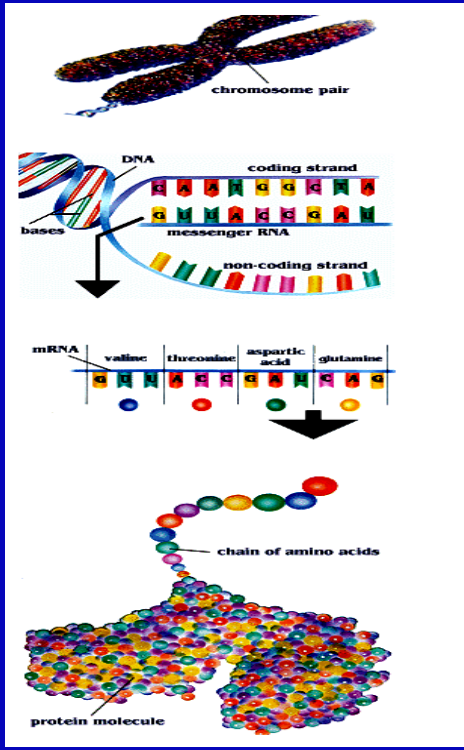
The pathways affected by HDAC activity.



Stimson L et al. Ann Oncol 2009;20:1293-1302

Annals of Oncology

A Winning Recipe



New discoveries

New Treatments

Better imaging

RESULTS!!!

We are closing in !