Lymphoma Biology, Treatment Options and Nutrition

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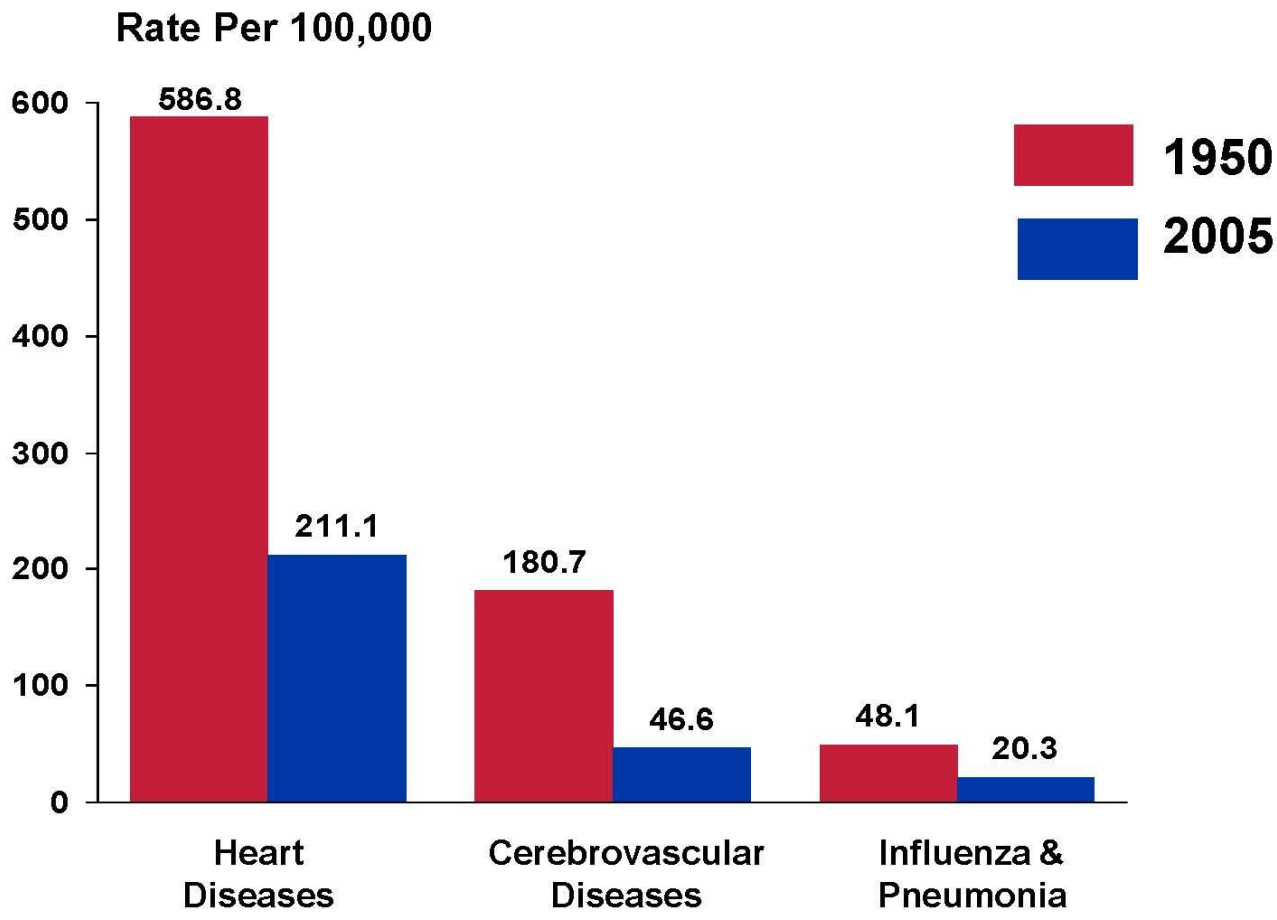
British Columbia Cancer Agency

University of British Columbia

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

Center for Lymphoid Cancer
Lymphoma
Myeloma
Leukemia

Change in the US Death Rates* by Cause, 1950 & 2005



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2005 Mortality Data: US Mortality Data 2005, NCHS, Centers for Disease Control and Prevention, 2008.

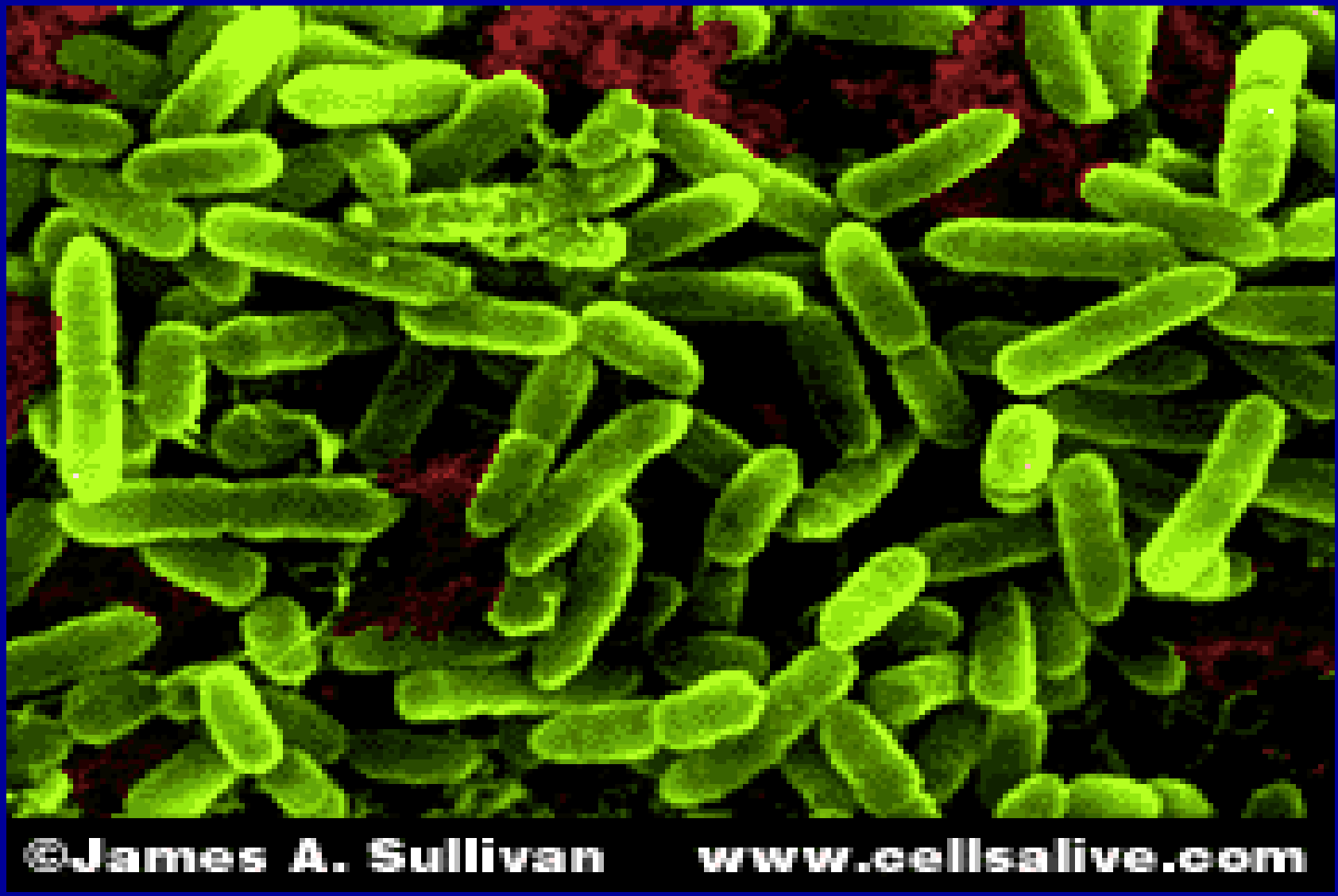
Cancer
Noteworthy World Statistics 2000s

- Incidence > 14,000,000
- Deaths > 8,500,000

- Leading cause of death in developed world
- 2nd leading cause of death in developing world

- In the developed countries
  Approximately 1 in 2 will develop cancer and
  1 in 4 will die from cancer
- The developing countries are rapidly catching up

- 11 most common cancers (~ 90% of all cancer)
- Prostate, breast, lung, colo-rectum, lymphoid, bladder, pancreas, kidney, uterus, thyroid, melanoma
- Only ONE is curable once metastatic: lymphoid cancer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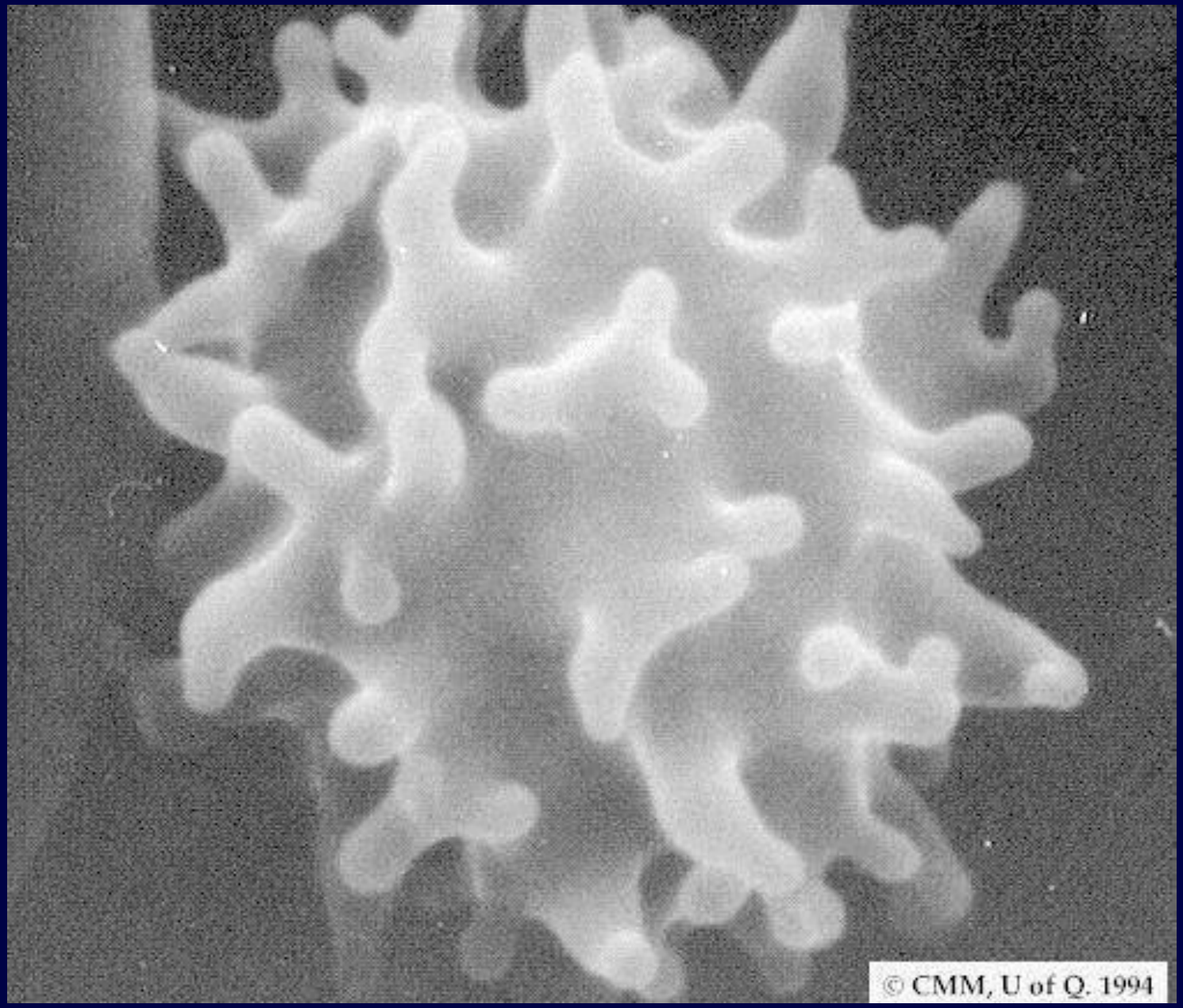
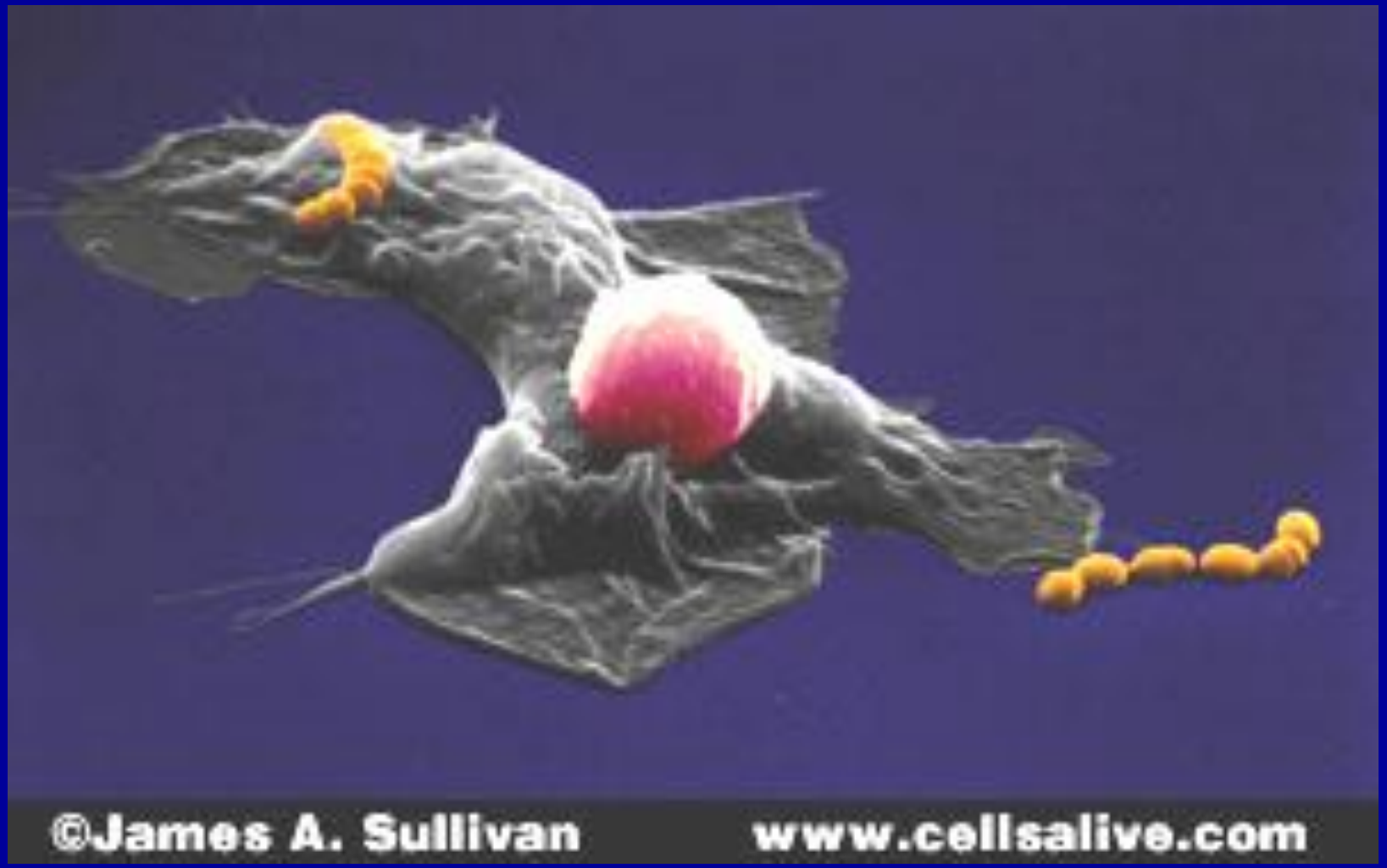
Lymphoid Cancer
What is it ?

- Our immune system is our defense system against the invaders of the world

Bacteria	childhood ear infections
Fungi	diaper rash
Viruses	flu
Protozoa	malaria
Parasites	pinworms


© CMM, U of Q. 1994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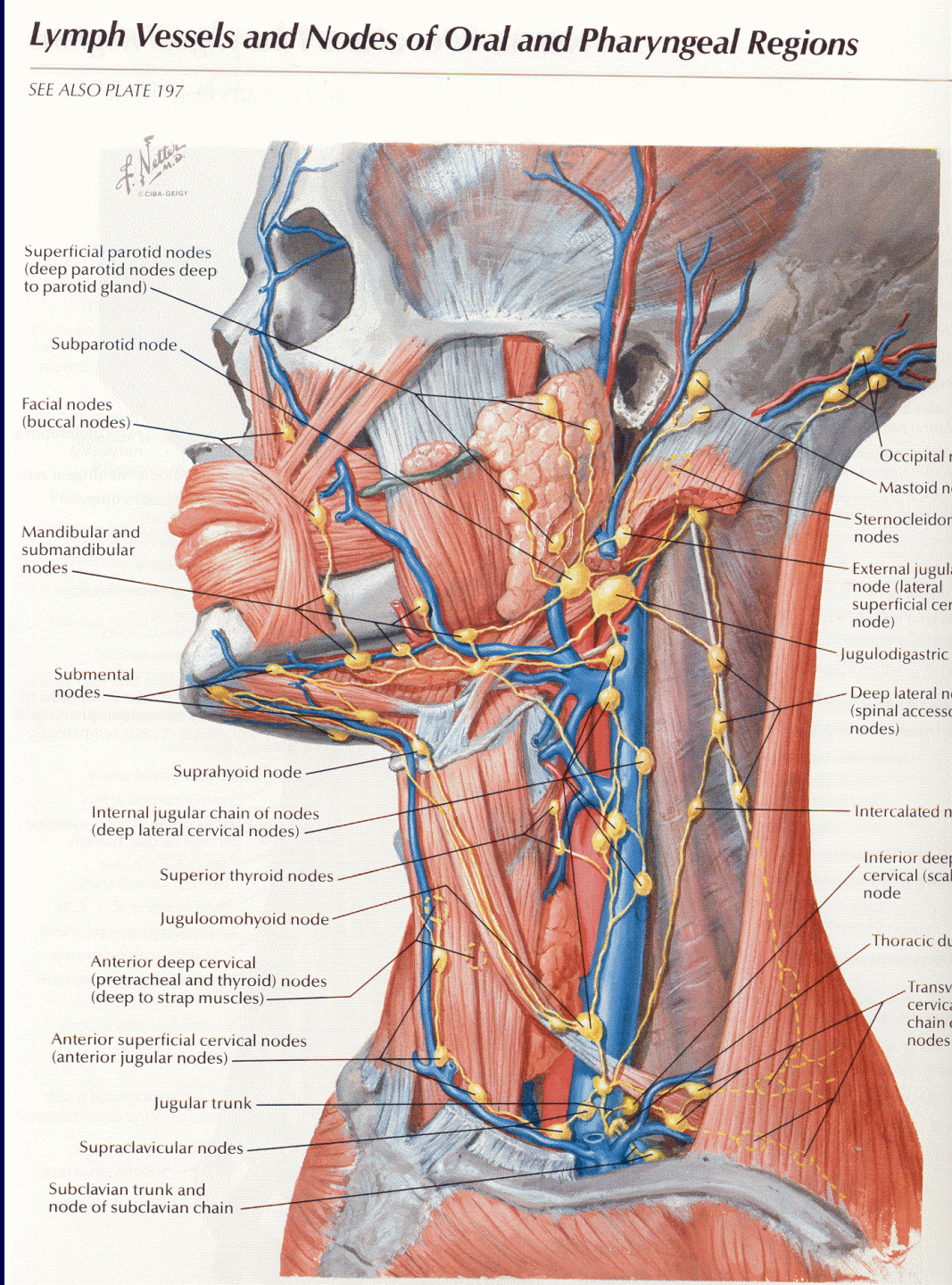
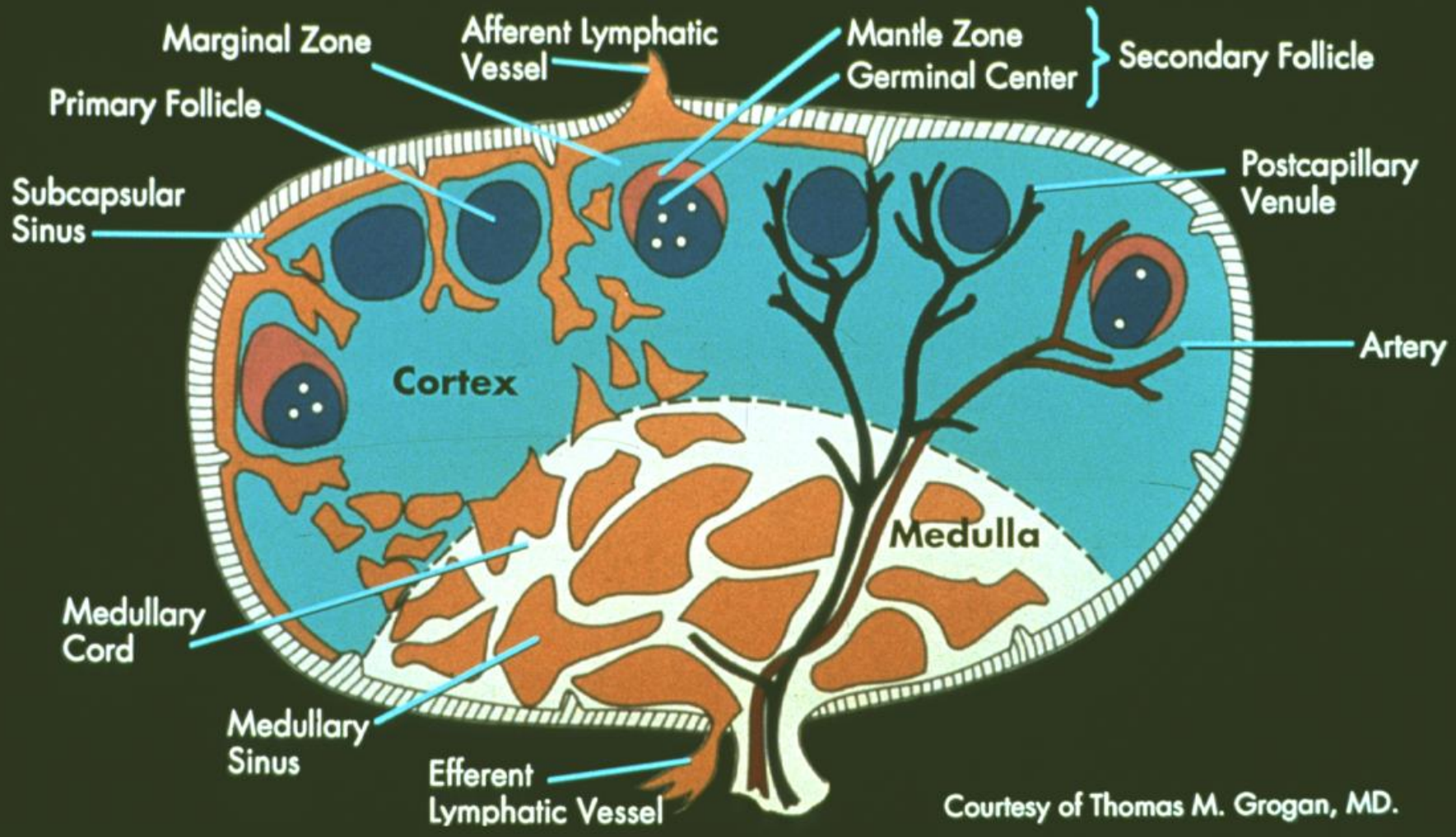
Lymph node distribution in the head and neck area showing close association with vasculature and neural structures

Netter, *Atlas of Human Anatomy* 1989

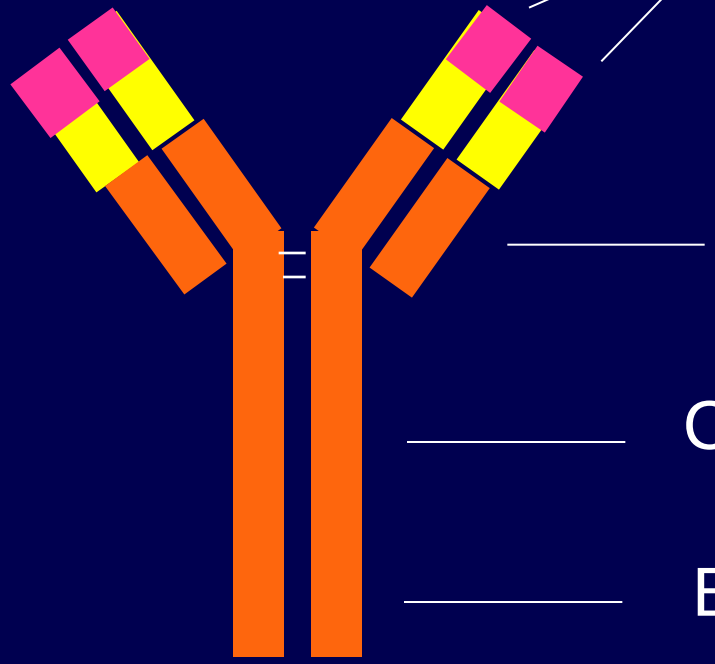


Lymph Node



Courtesy of Thomas M. Grogan, MD.

Basic Antibody Structure



Specific binding sites = variable region

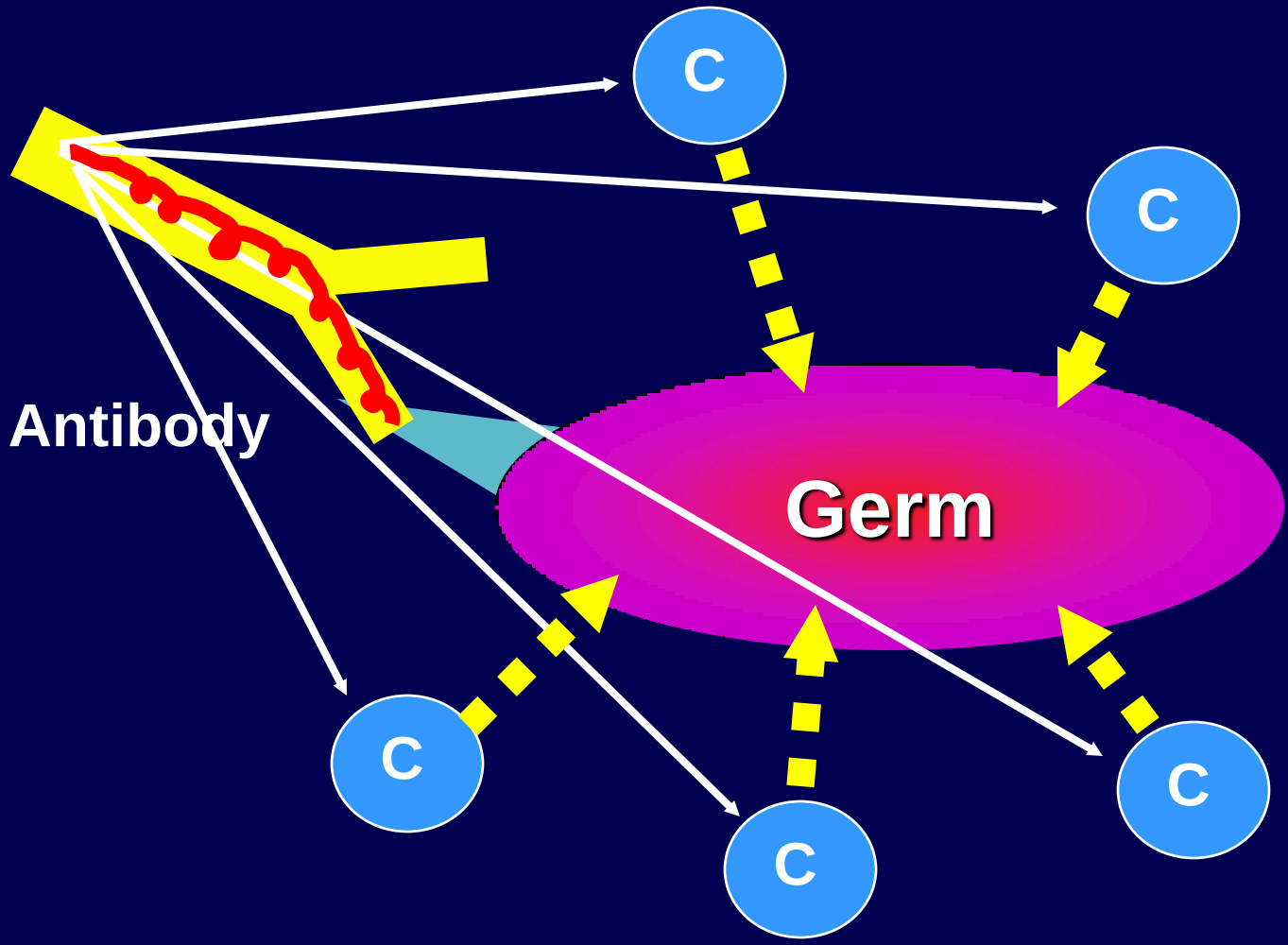
Constant region

Complement activation region

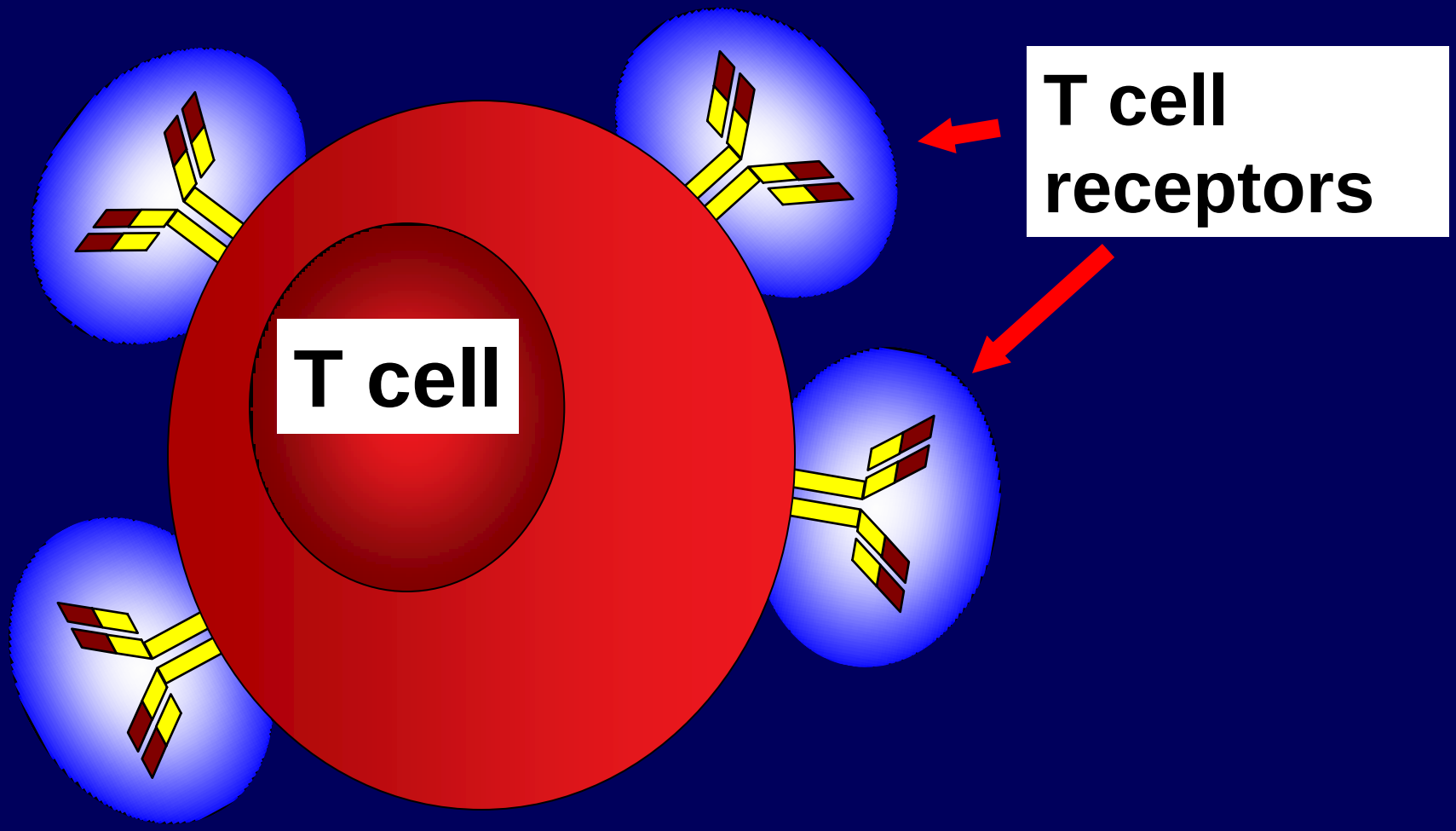
Binding site to effector cells

Adapted from Rybak, *Proc Natl Acad Sci USA,* 1992;89:3165

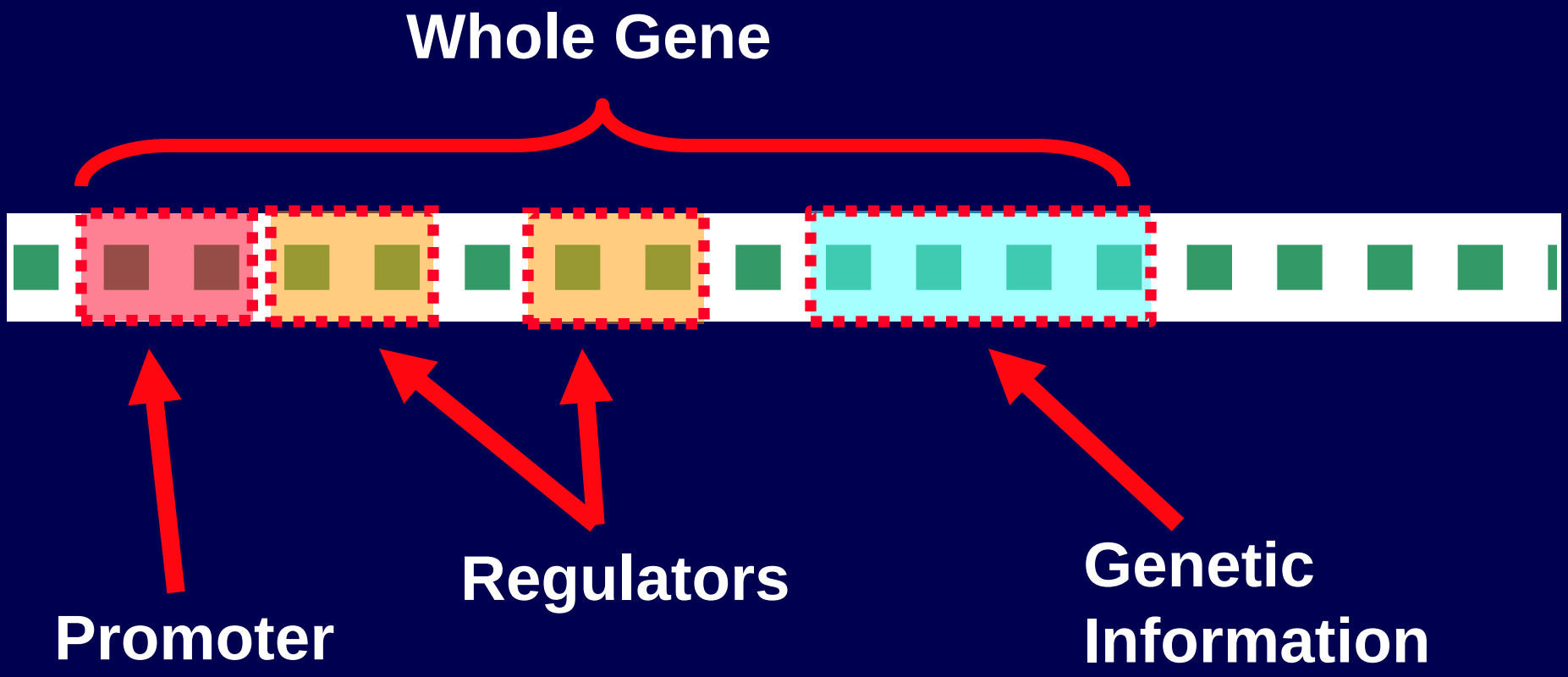
Basic Mechanism of Antibody Action



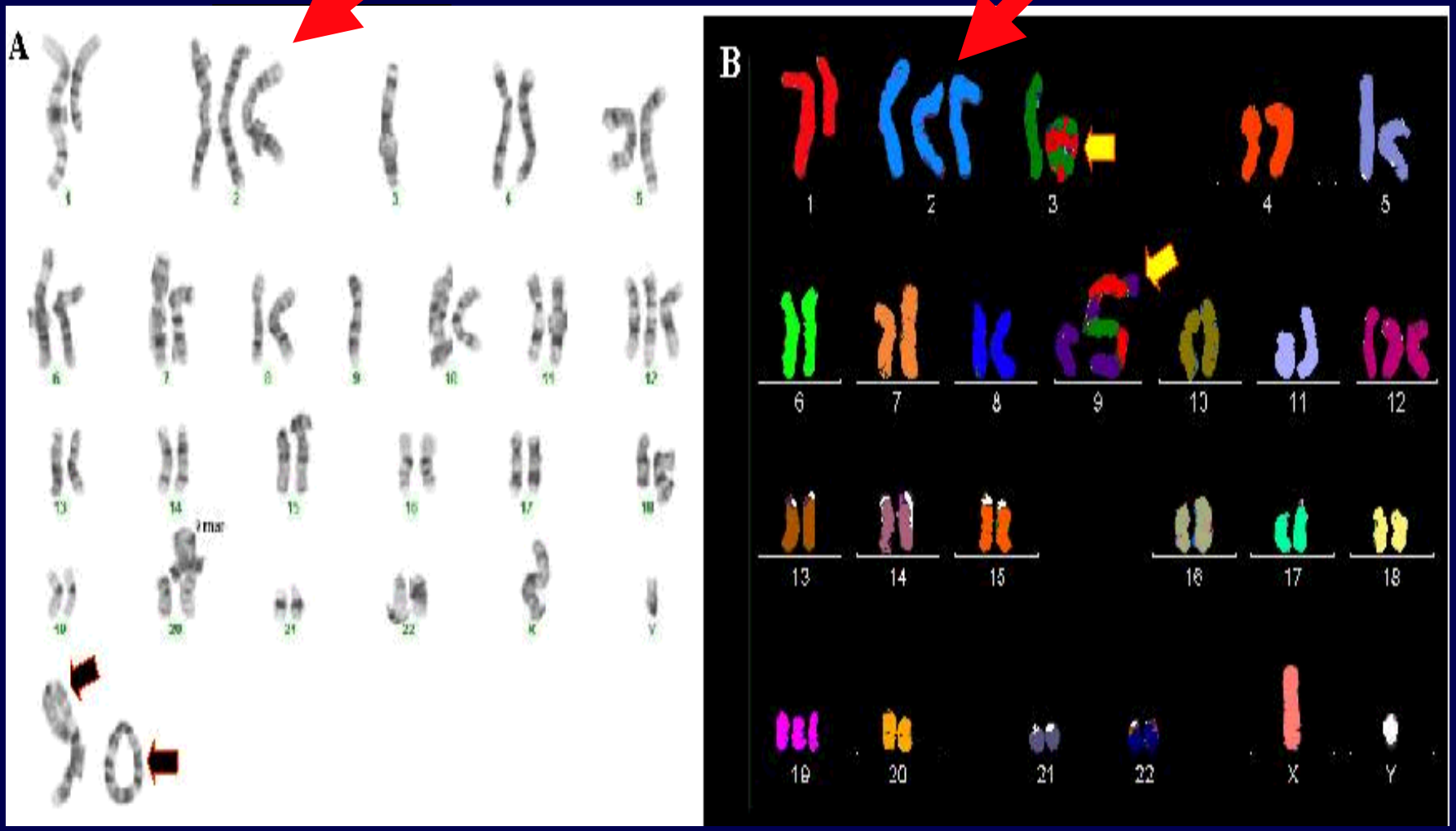
T Cell Structure

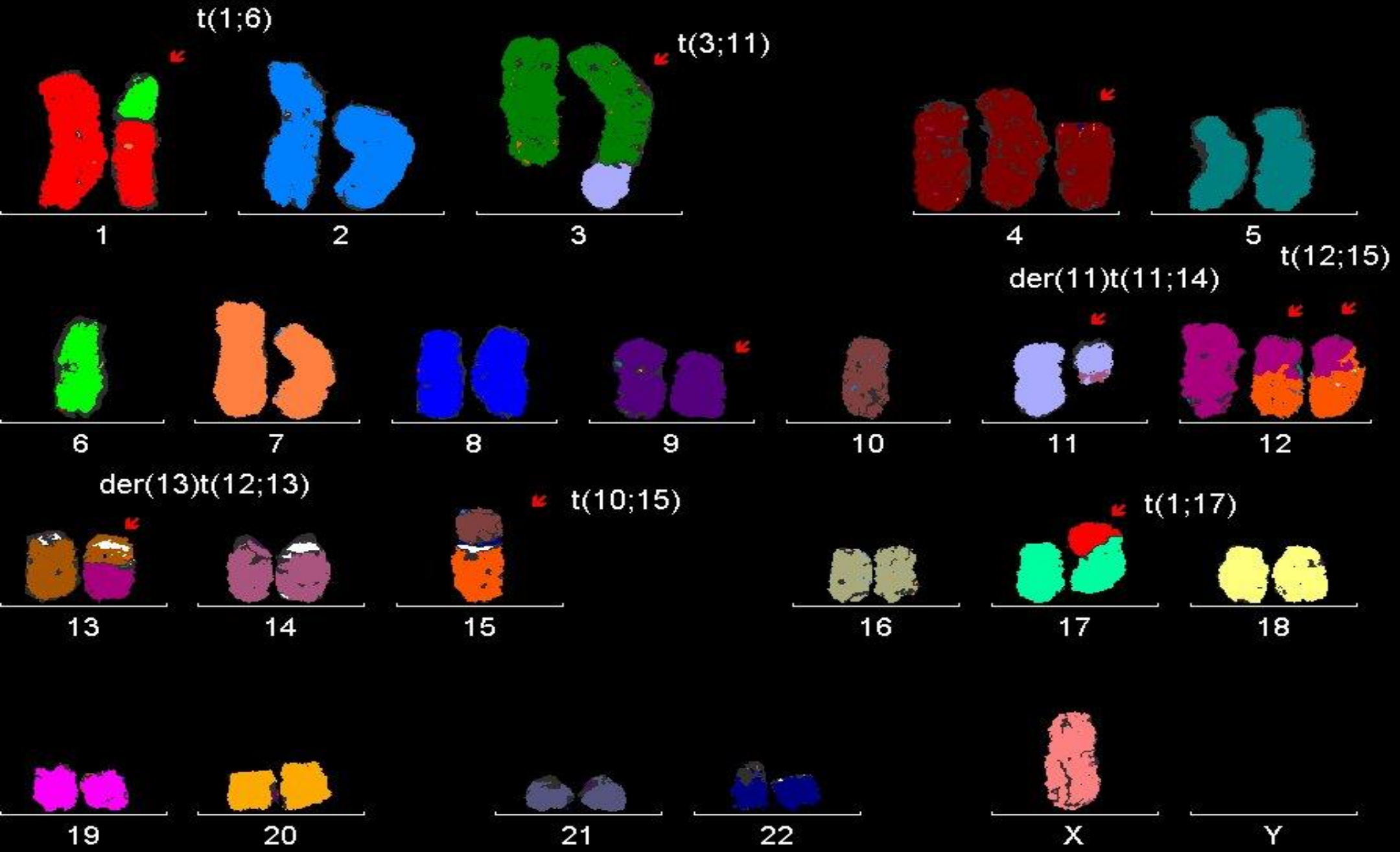


Basic Gene Structure and Control



Duplication = trisomy




t(1;6)
t(3;11)
1
2
3
4
5
t(12;15)
der(11)t(11;14)
6
7
8
9
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der(13)t(12;13)
t(10;15)
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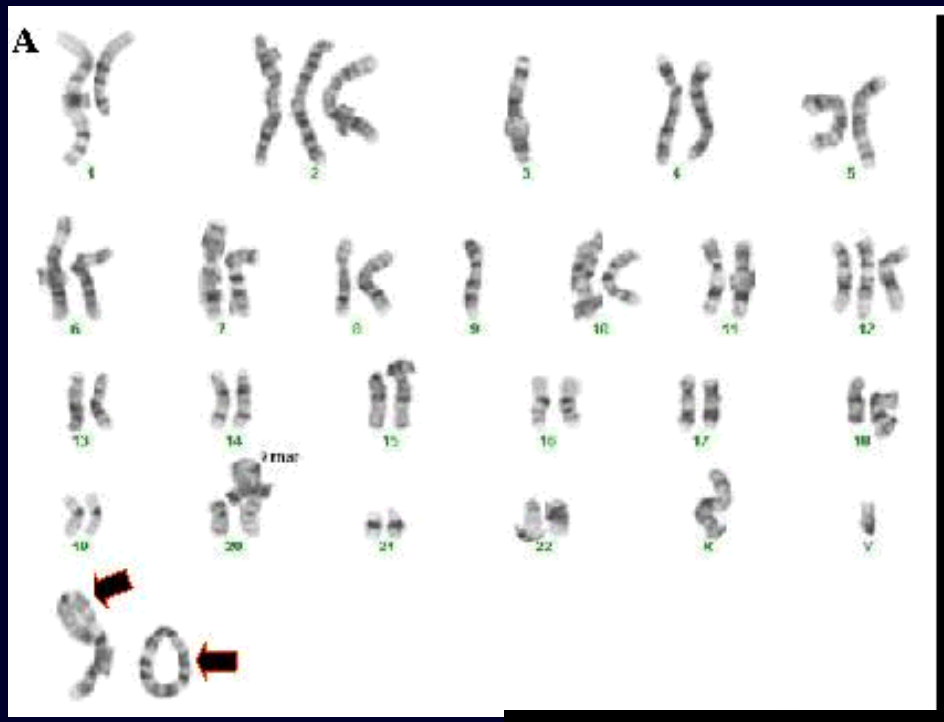
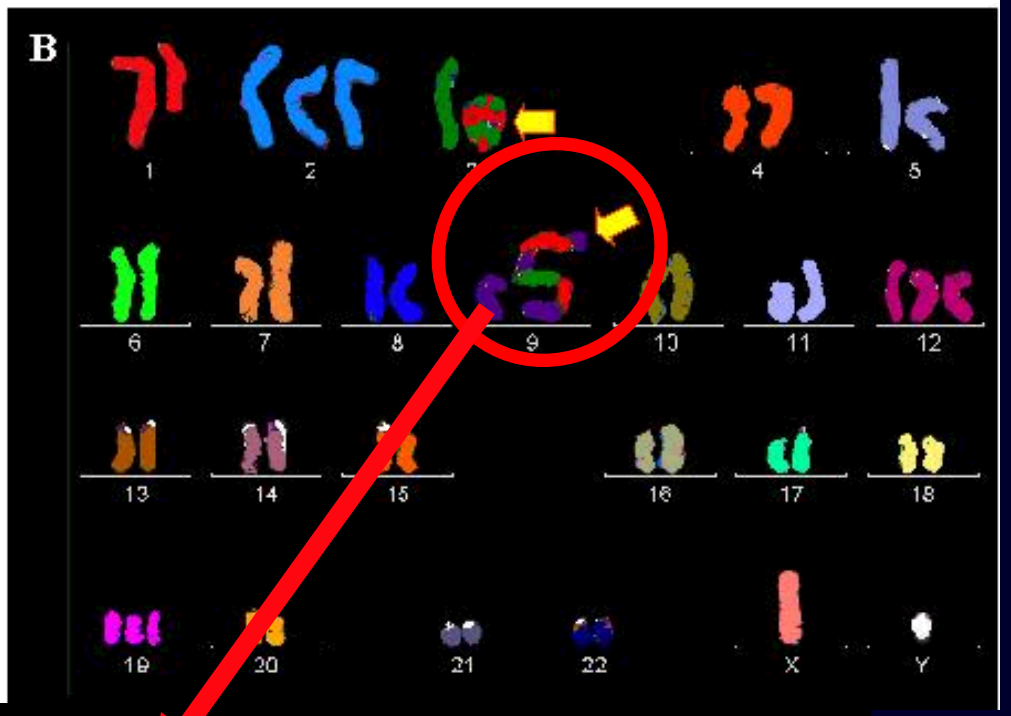
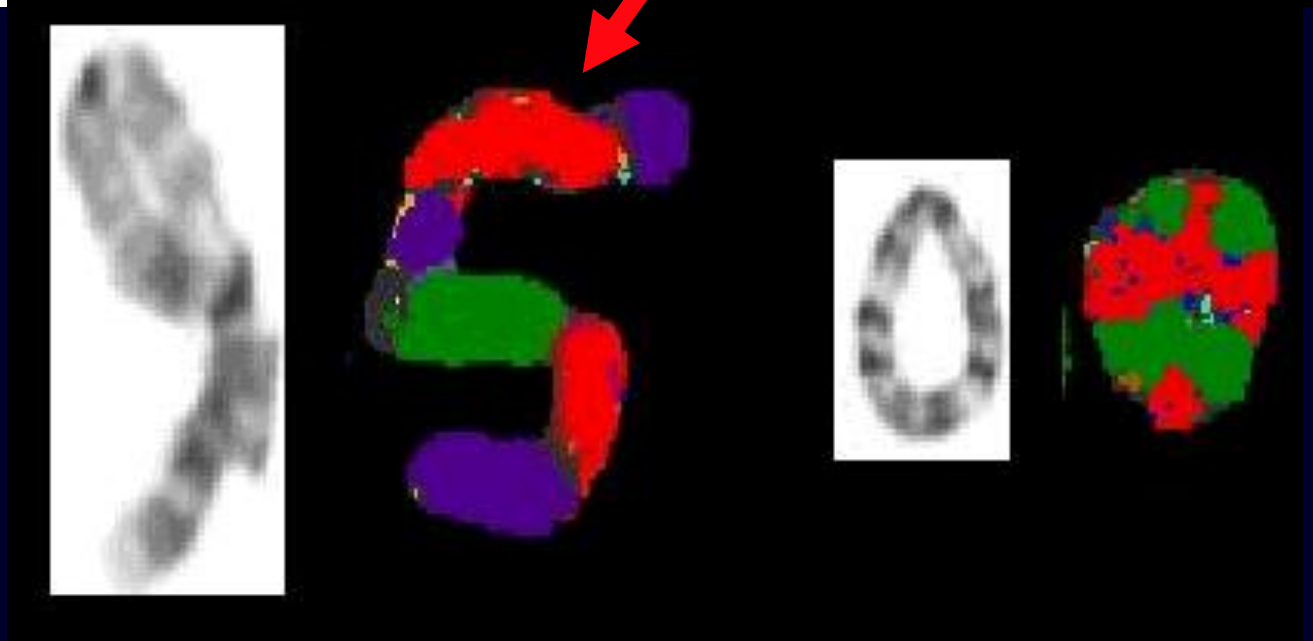
21
22
X
Y

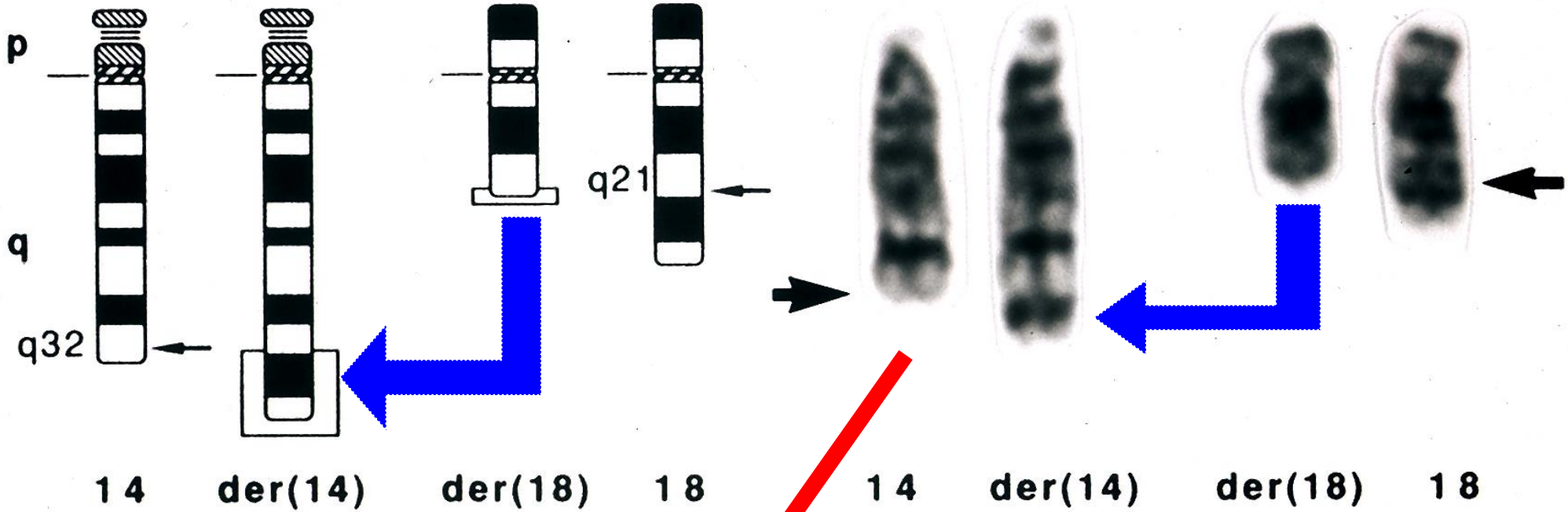
MFISH - complex karyotype





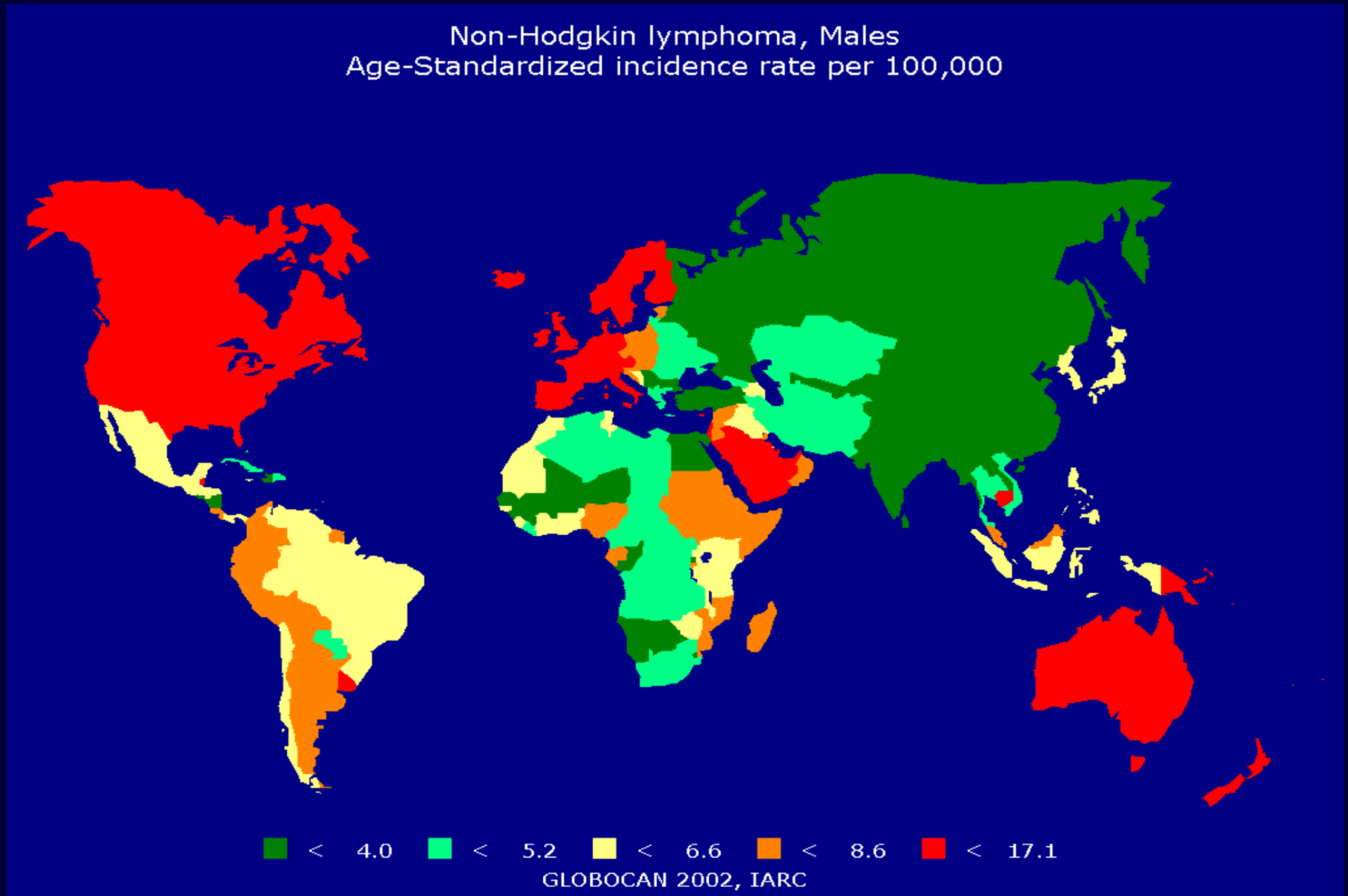


Follicular Lymphoma, t(14;18)(q32;q21)

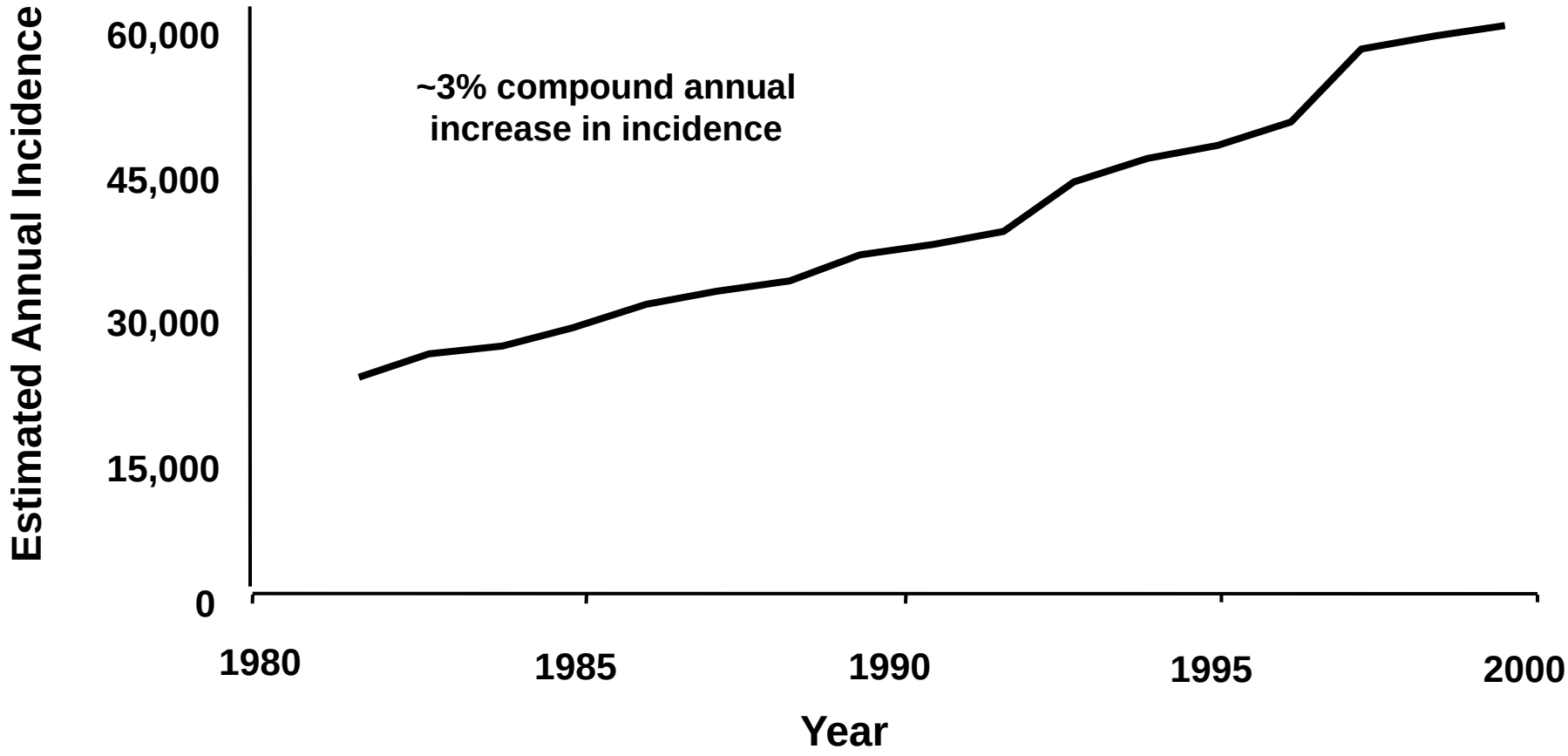


BCL2 overproduction

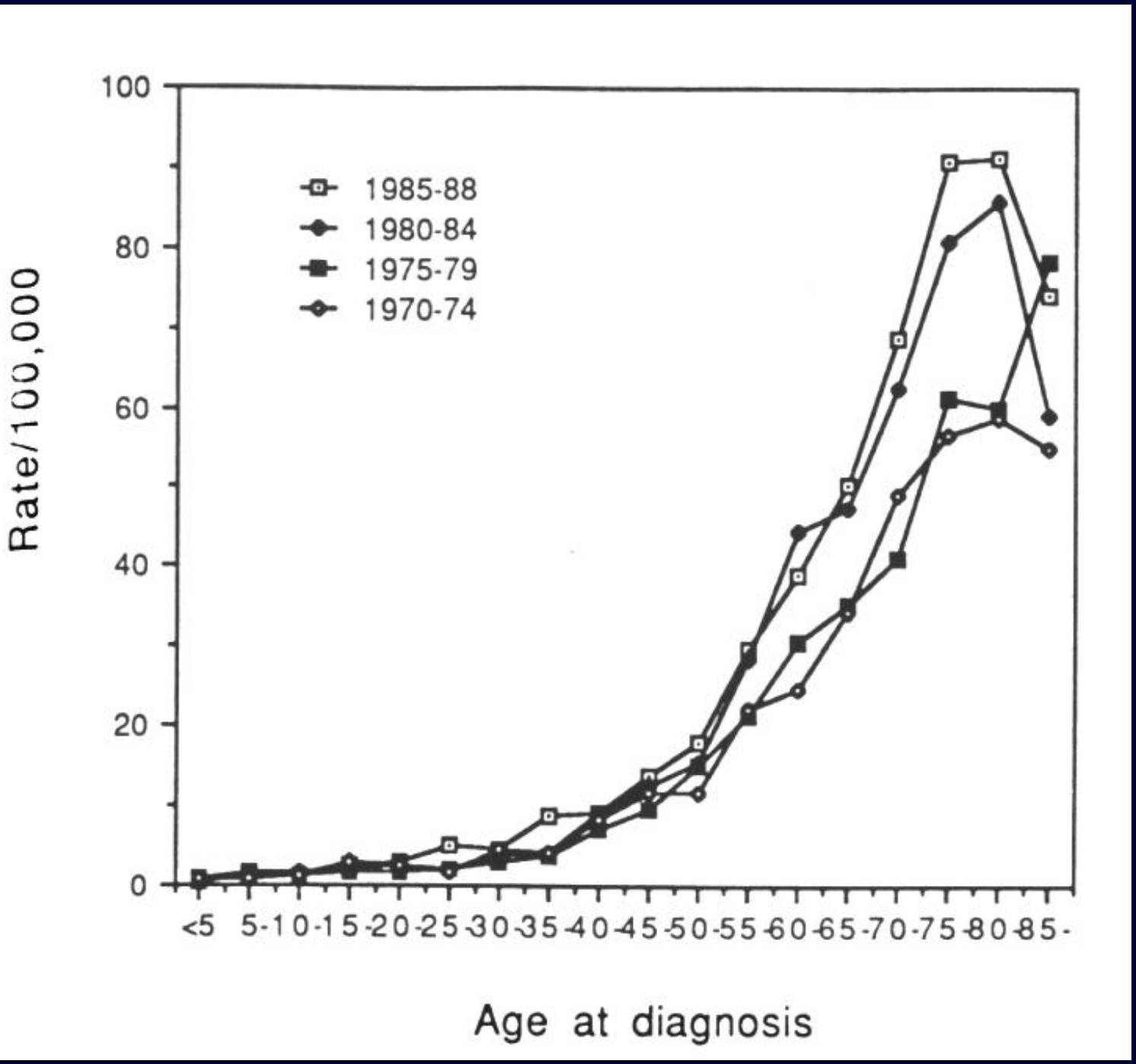
Lymphoid Cancer Worldwide Variation



Estimated Incidence of Non-Hodgkin Lymphoma in North America



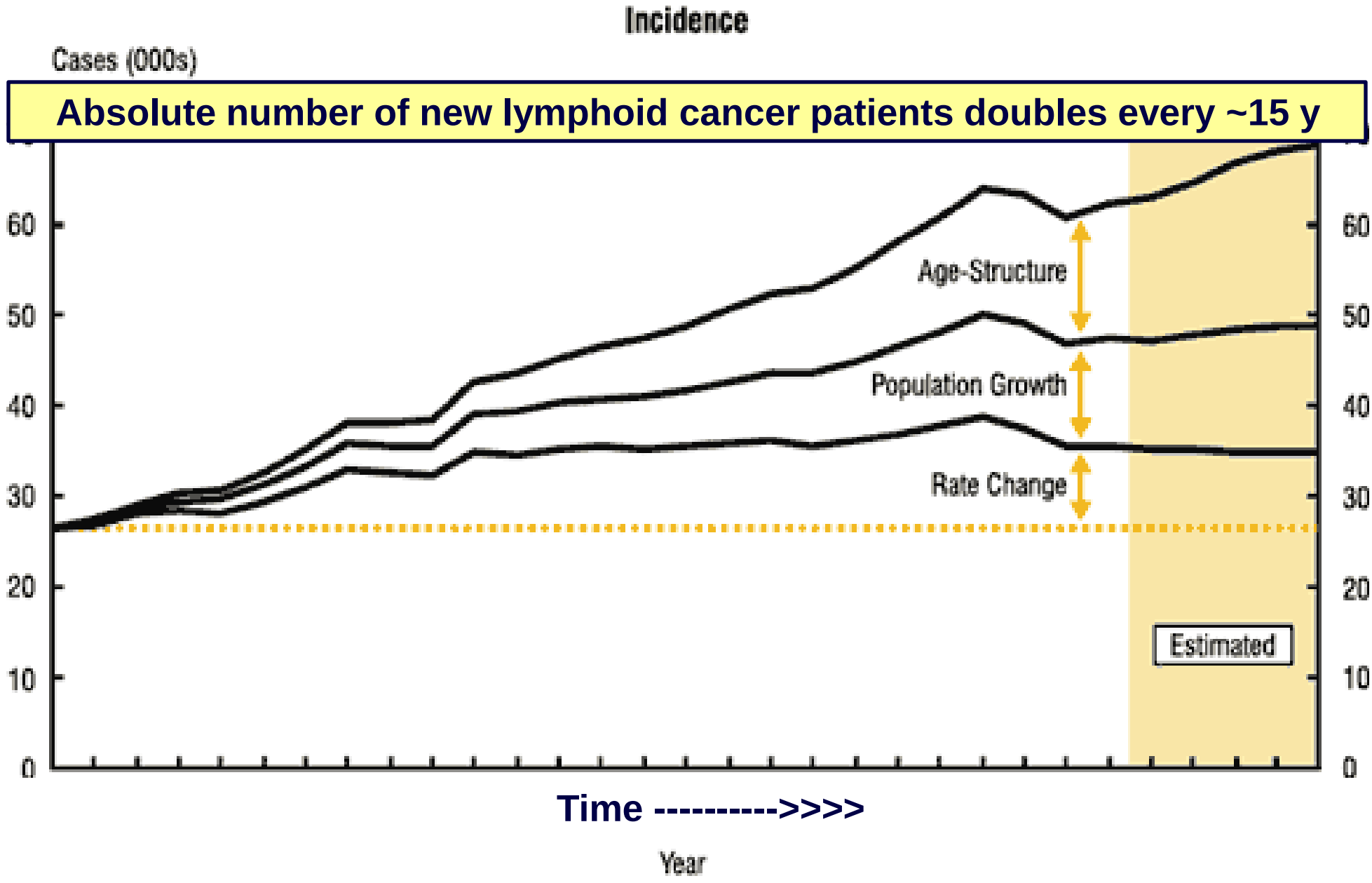
Adapted from Greenlee et al. *CA Cancer J Clin.* 2001;51:15.



Non-Hodgkin Lymphoma

Incidence by Age

Zheng, Cancer, 1992;70:840

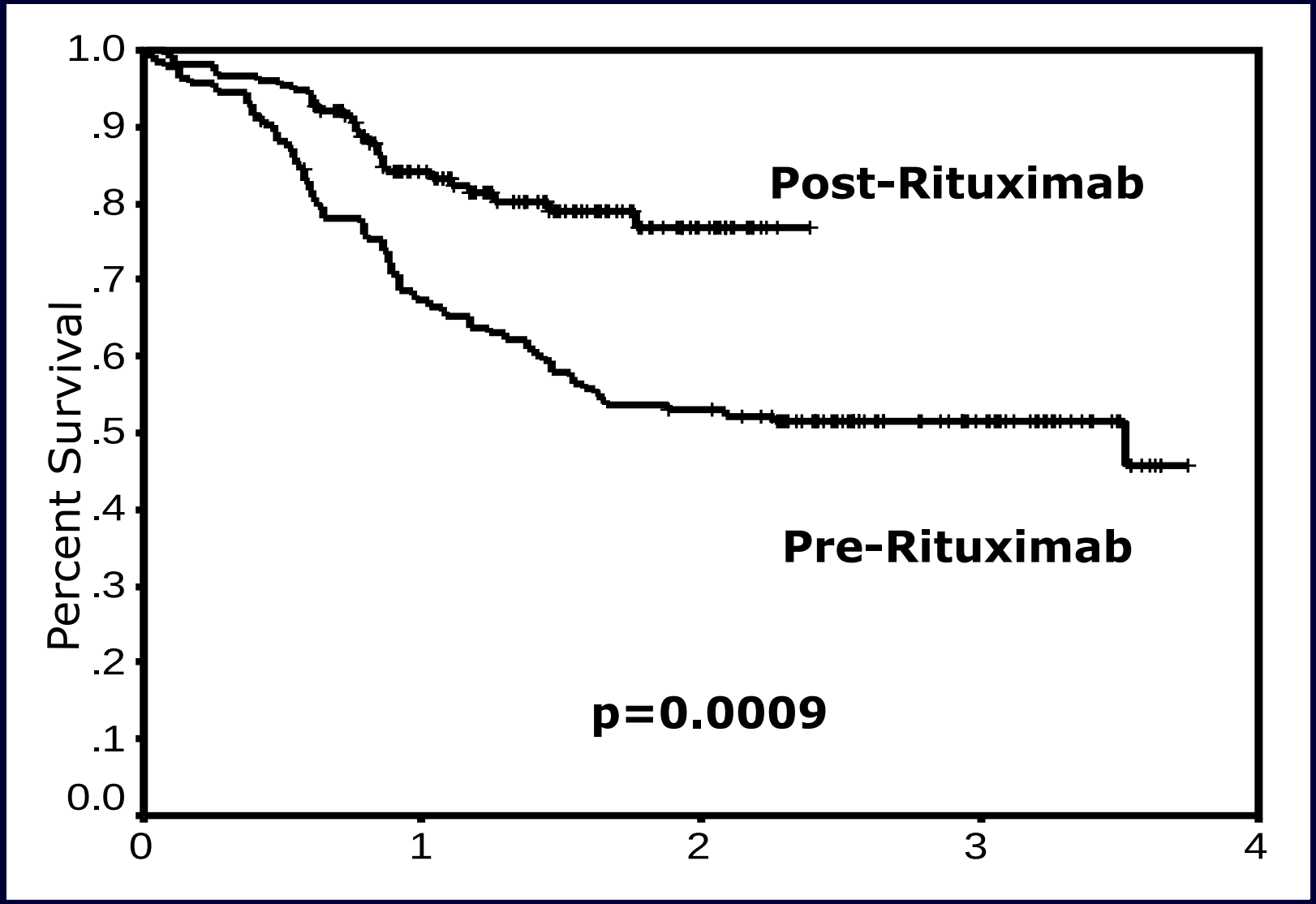

Incidence
Cases (000s)
Absolute number of new lymphoid cancer patients doubles every ~15 y
60
50
40
30
20
10
0
Age-Structure
Population Growth
Rate Change
Estimated
Time ---------->>>>
Year

Evolution of Treatment of NHL
Diffuse Large B cell Lymphoma as an Example

- 1970s Incurable, median survival ~ 6 months
- 1970s Borrowed empiric chemoTx from Hodgkin lymphoma
  Cure ~ 35 %
- 1980-90s Improved classification, supportive care
  Cure ~ 50 %
- 1980-90s 10^6s of $; 10^3s clinical trial patients; 12s of "new" chemoTx regimens
  Cure ~ 50 %
- 2000s Add monoclonal Ab (rituximab), more 10^6s/1000s/12s
  Cure ~ 70 %

- 1980-2010 spent 10^2 x 10^6 $, in 10^2 clinical trials enrolling 10^3 patients to add one agent and go from 50 % to 70 % survival

Overall Survival by Treatment Era (n = 294)



Lymphoid Cancer: How Research Improves Treatment

Treatment old way

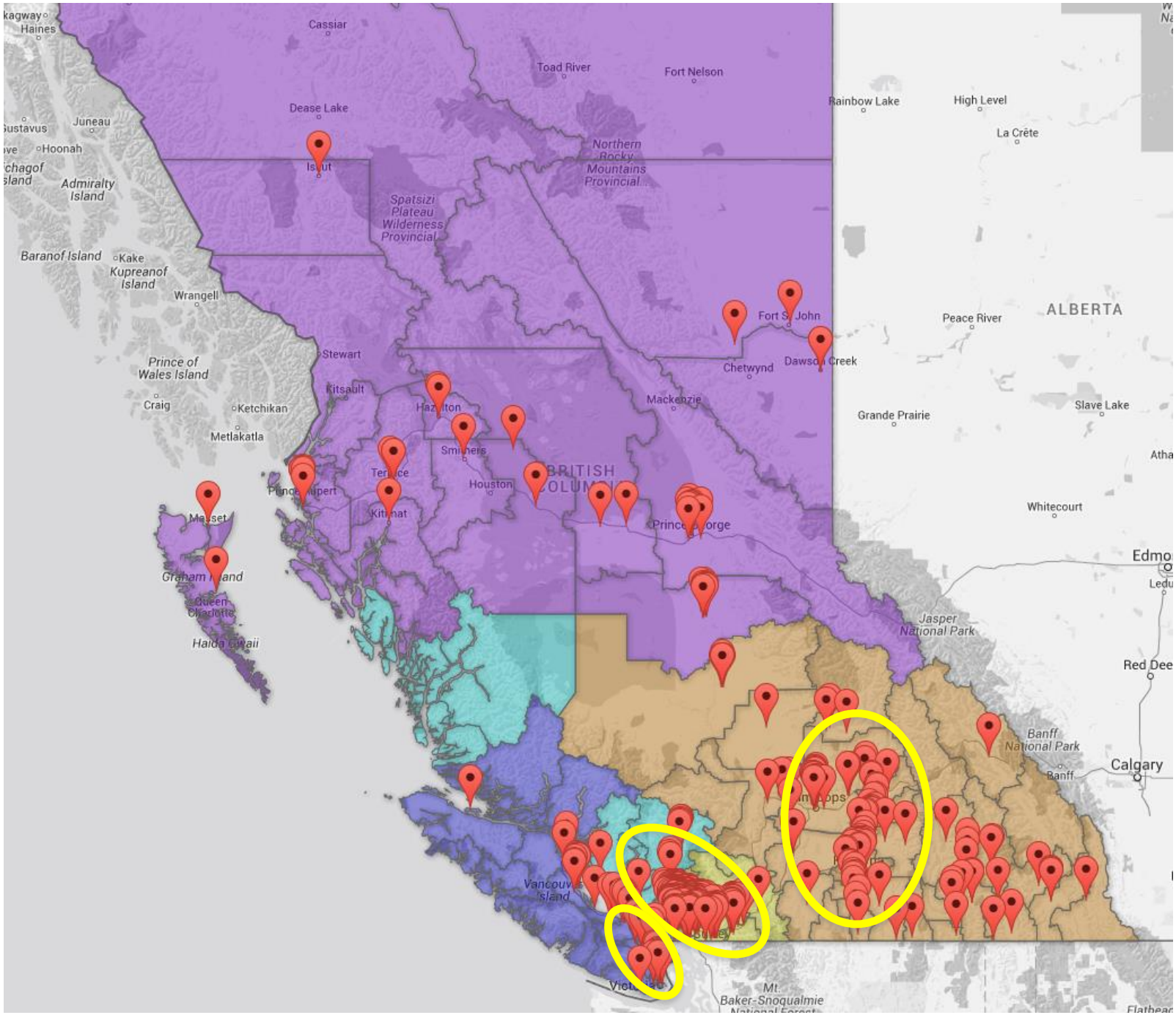
- Empiric
- Asso
- Non
- Toxi
- No p

Necessary

- Deeper understanding of fundamental genetic control of neoplastic cells = ultrafine detail genomics
- Somatic - Identification of key control elements
- Constitutional – predisposing genetic characteristics

ıre

- Non-toxic
- Prevention & early detection enabled by genotype recognition

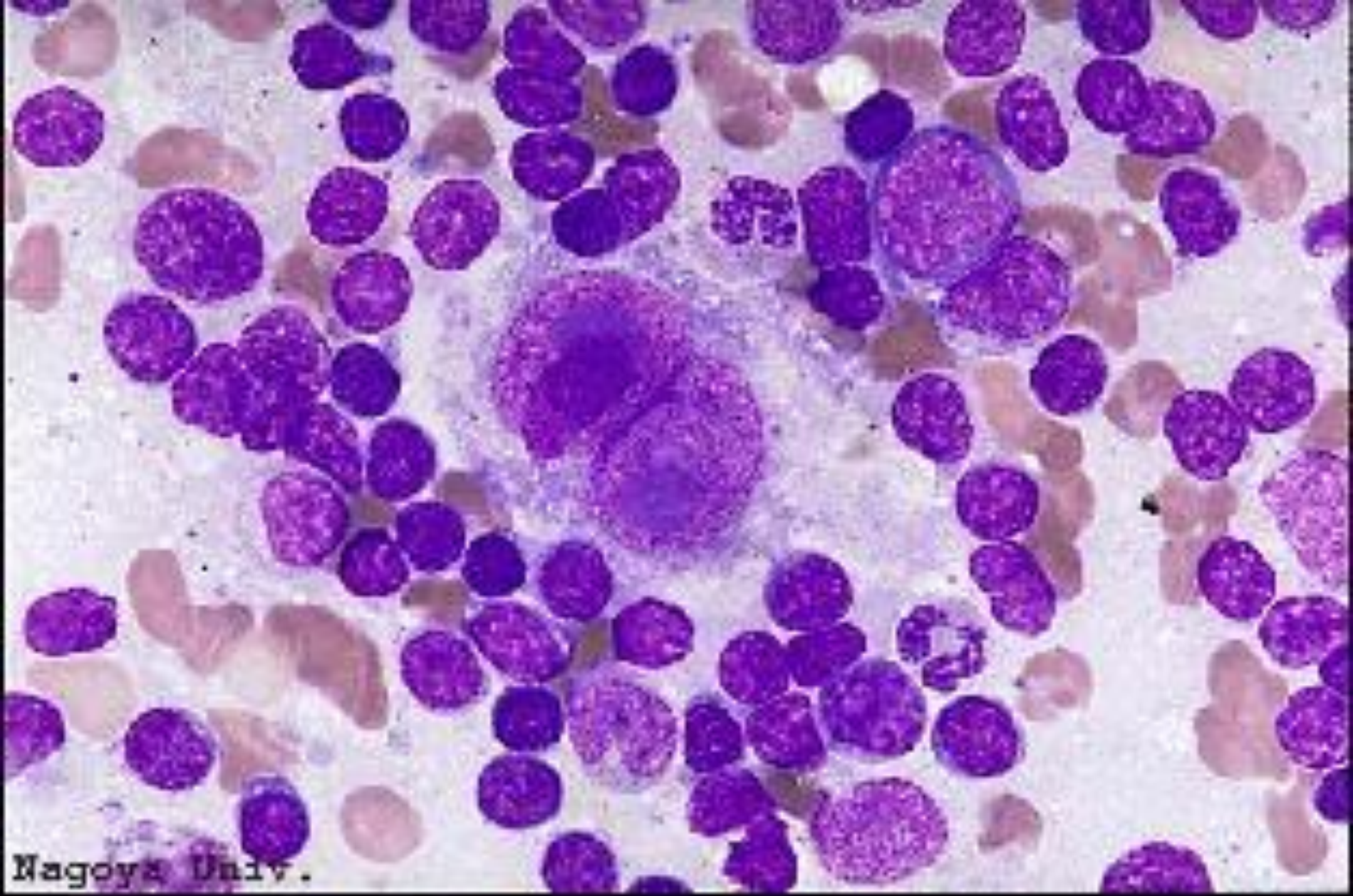


- Northern Health
- Interior Health
- Fraser Health
- Vancouver Coastal Health
- Island Health

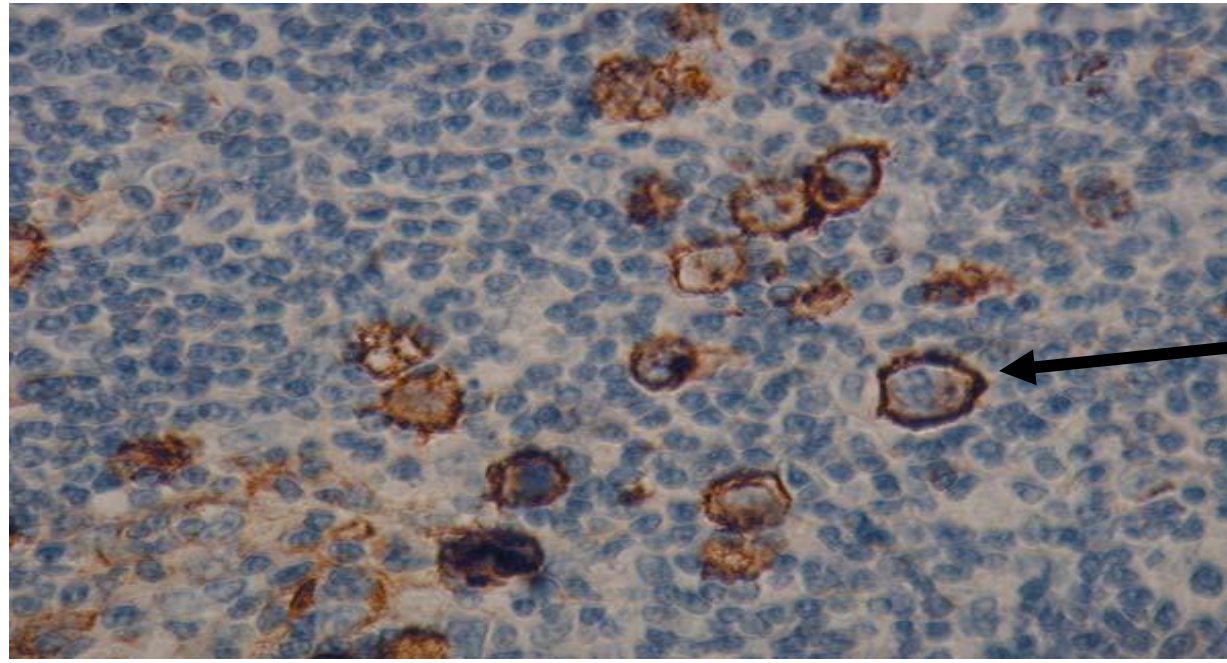
= **Home location of individual participant**

= **~75% of provincial population**

Hodgkin Lymphoma


Nagoya Univ.

CD30: A Rational Target in HL

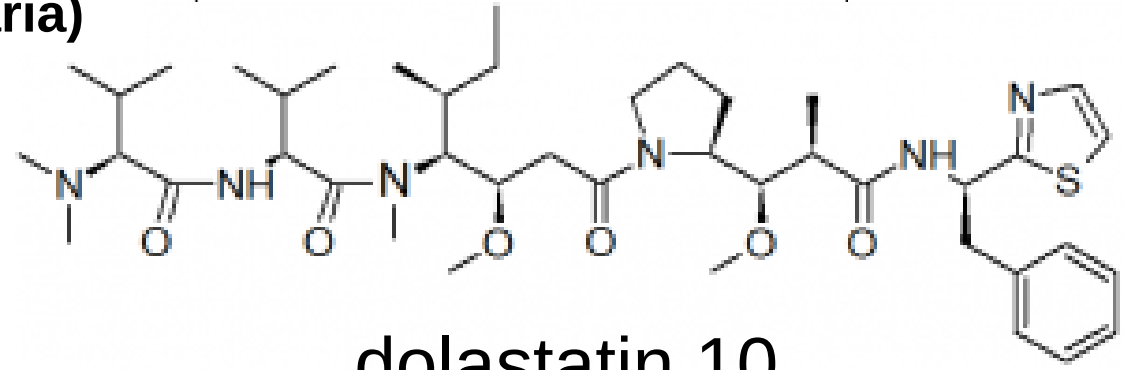


- Expressed on virtually all HRS cells[1]
- Very low expression on normal cells[2]
- In healthy tissue, limited to small numbers of activated B and T lymphocytes and natural killer cells[2]

1. Stein H, *Blood* 1985;66:848-858
2. Durkop H, *J Pathol* 2000;190:613-618

Slide courtesy of Seattle Genetics

Japanese Sea Hare (Dolabella auricularia)

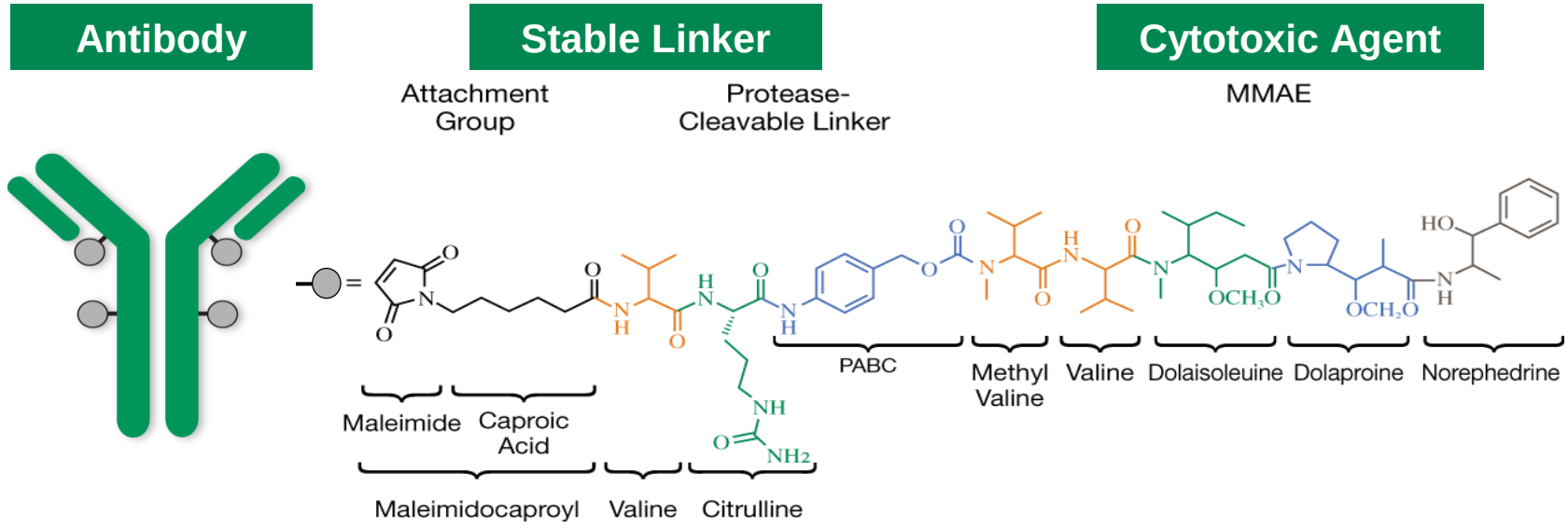


dolastatin 10

Secret: dolastatins are in fact produced by the cyanobacteria *Symploca hydnoides* and *Lyngbya majuscula*, which are part of the sea hare's diet.

ADC Technology: Brentuximab Vedotin (Adcetris®)

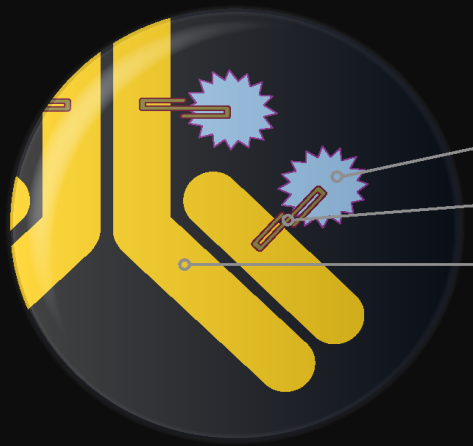
- **Brentuximab-vedotin consists of 3 components[1,2]**
  - **The antibody cAC10, specific for human CD30**
  - **A protease-cleavable linker that covalently attaches MMAE to cAC10**
  - **Monomethyl auristatin E (MMAE), is an anti-microtubule agent**



1. Okeley, *Clin Cancer Res.* 2010;16:888-897
2. Doronina, *Nat Biotechnol.* 2003;21:778-784

Slide courtesy of Seattle Genetics

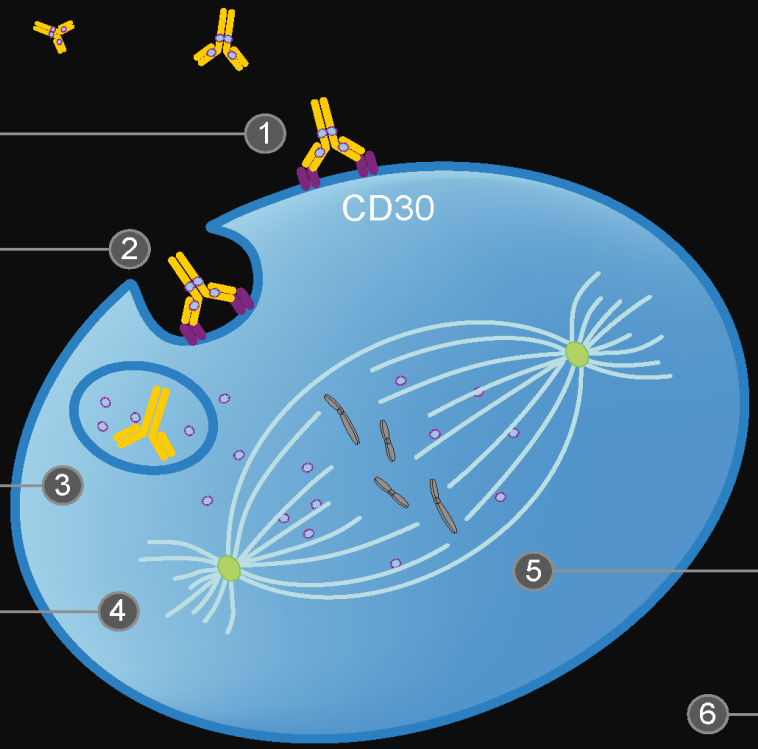
Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin antibody-drug conjugate (ADC)

- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody

Release of immunogenic cellular components



1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

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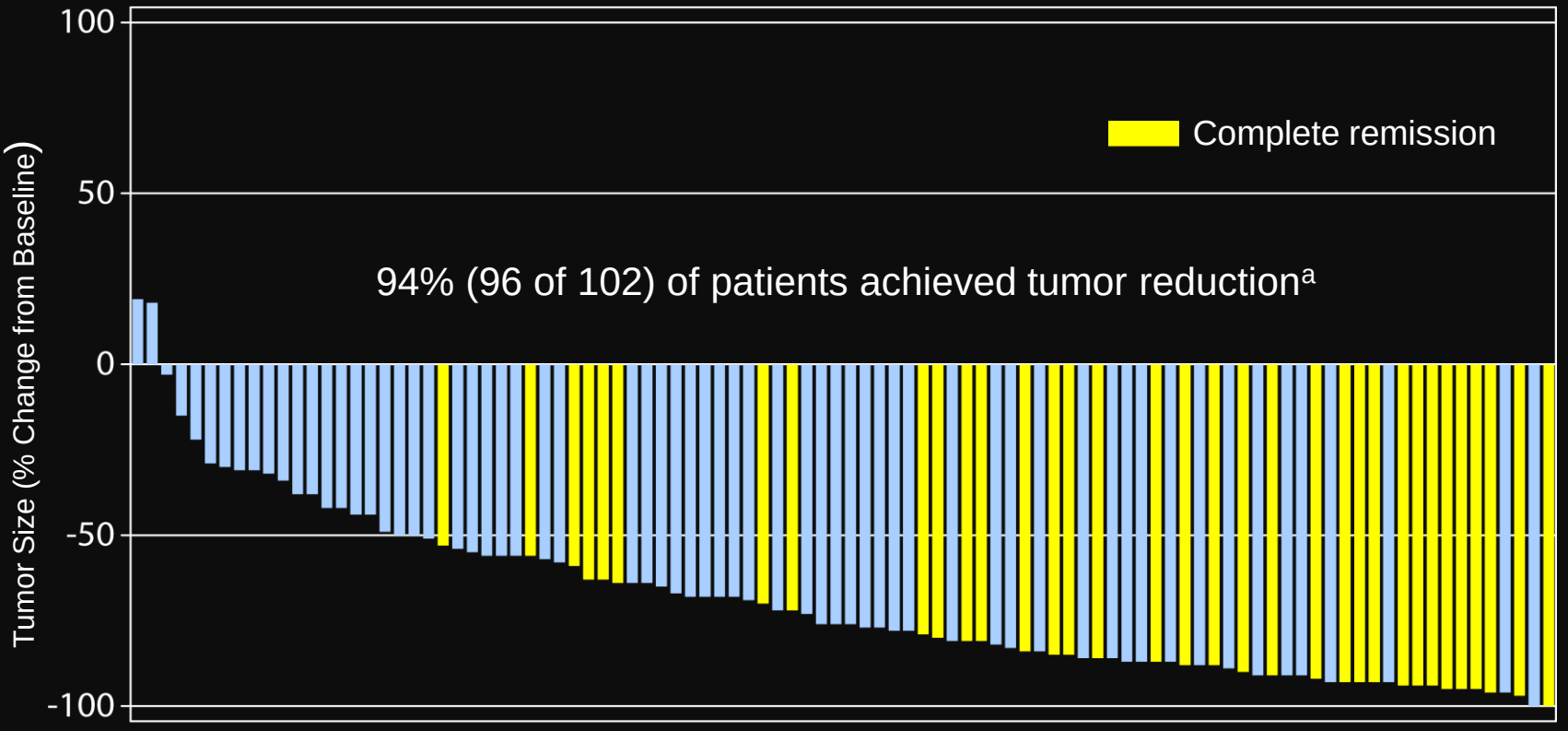
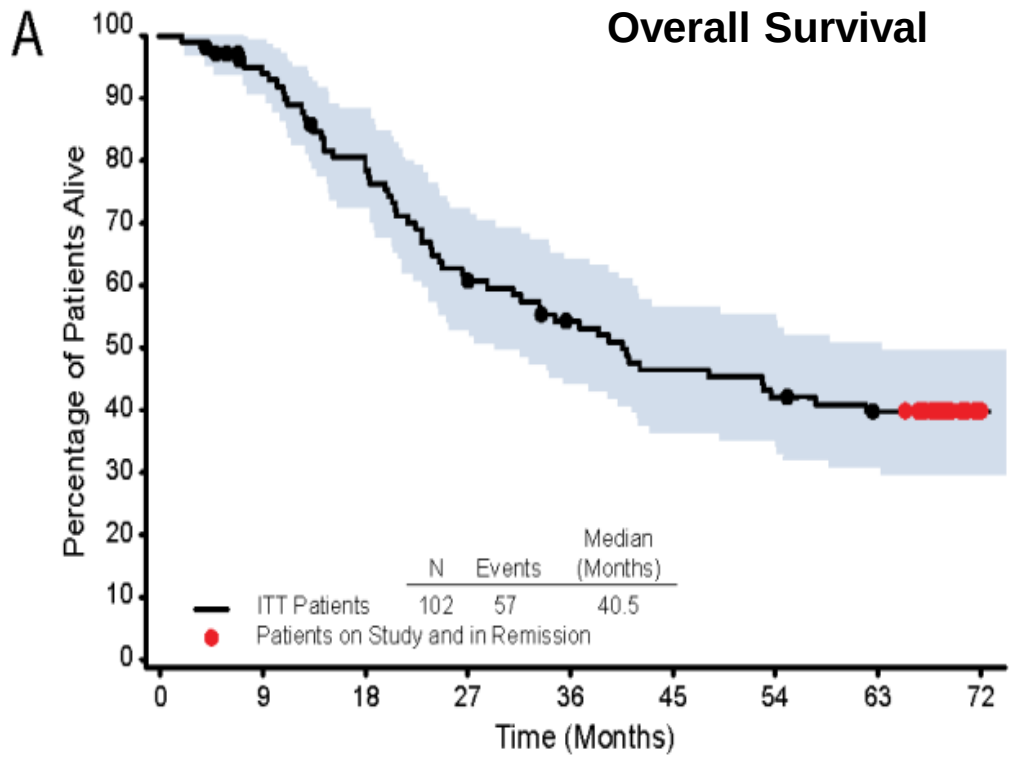
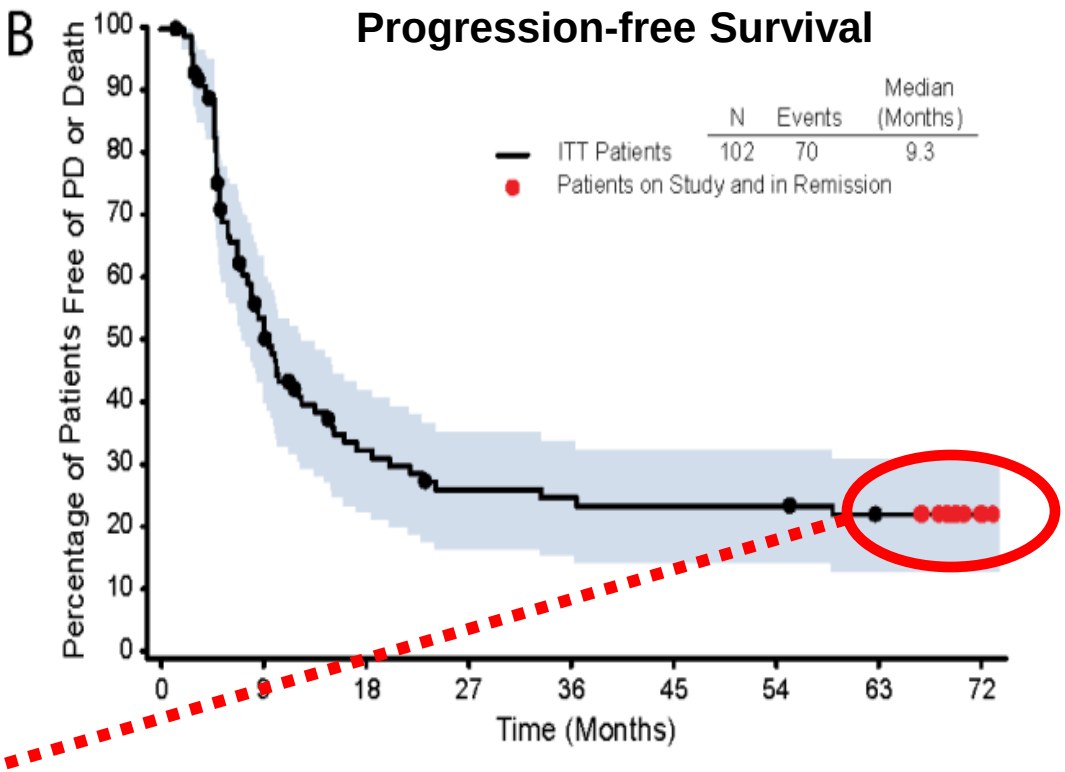
Brentuximab Vedotin in Relapsed/Refractory HL

- **Pivotal study in 102 pts with relapsed/refractory HL after ASCT**
- **75% objective response rate with brentuximab vedotin**
- **34% complete response rate**



Brentuximab Vedotin in Relapsed/Refractory HL





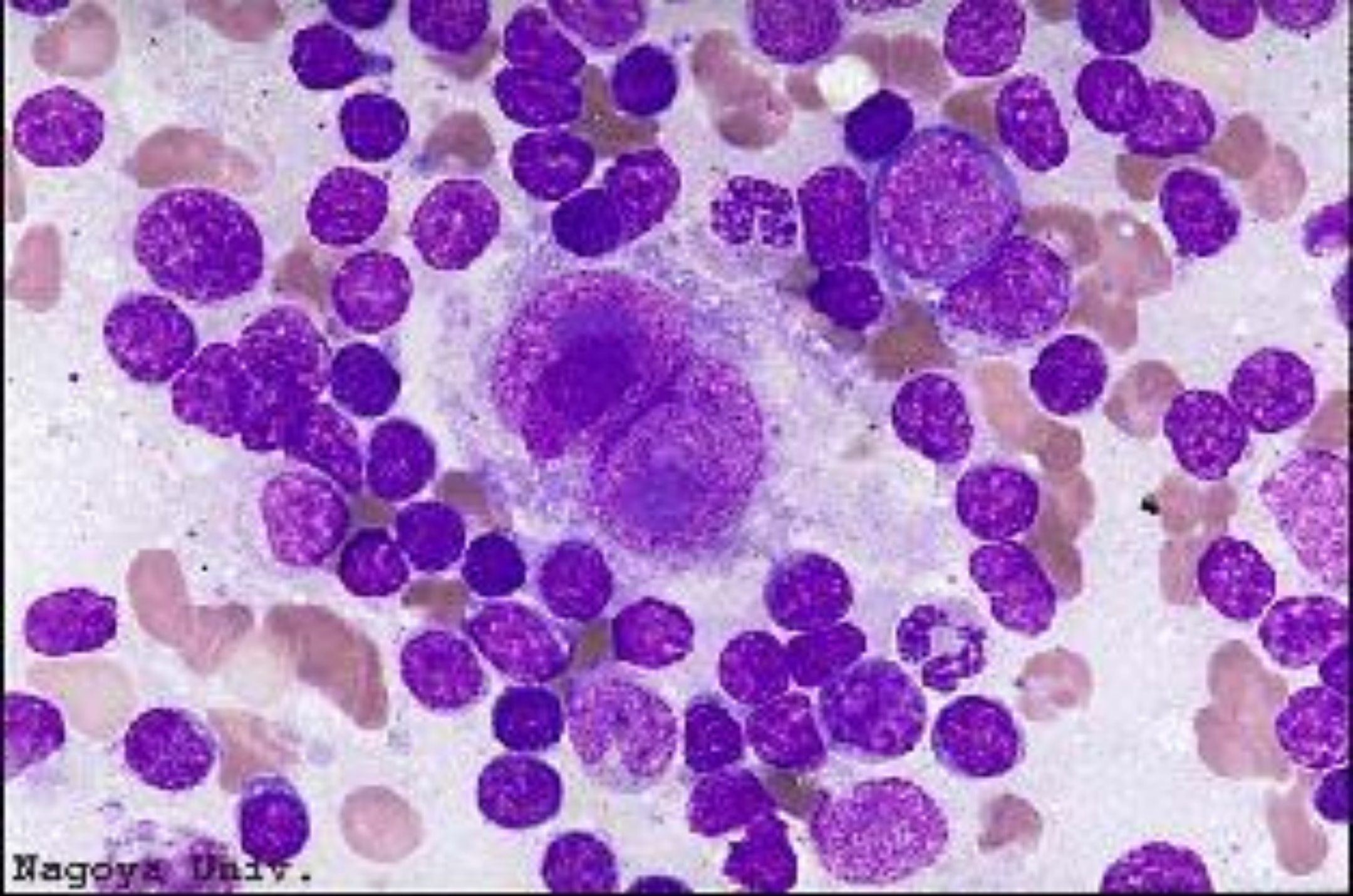
n = 13

4 transplant after Bv

9 no addn'l Tx

> 9% overall and almost 40% of CRs may have been cured with brentuximab vedotin alone

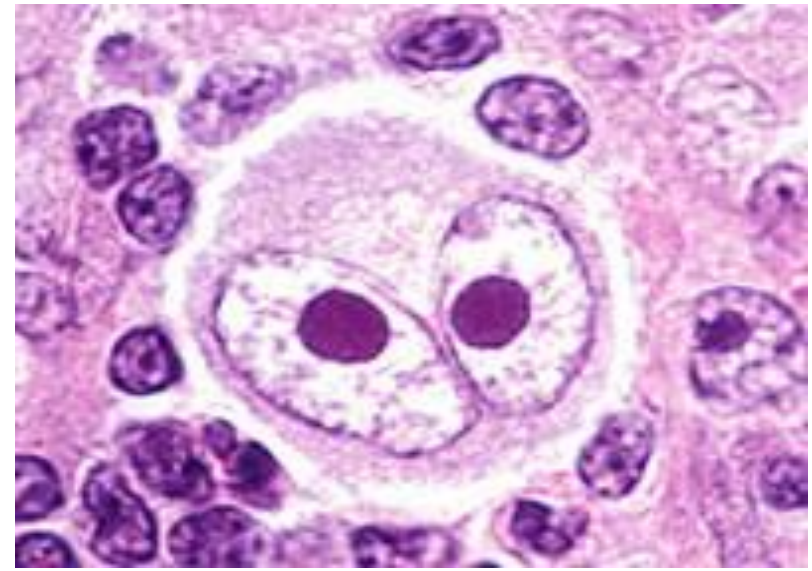
Chen, *Blood* 2016;128:1562


Nagoya Univ.

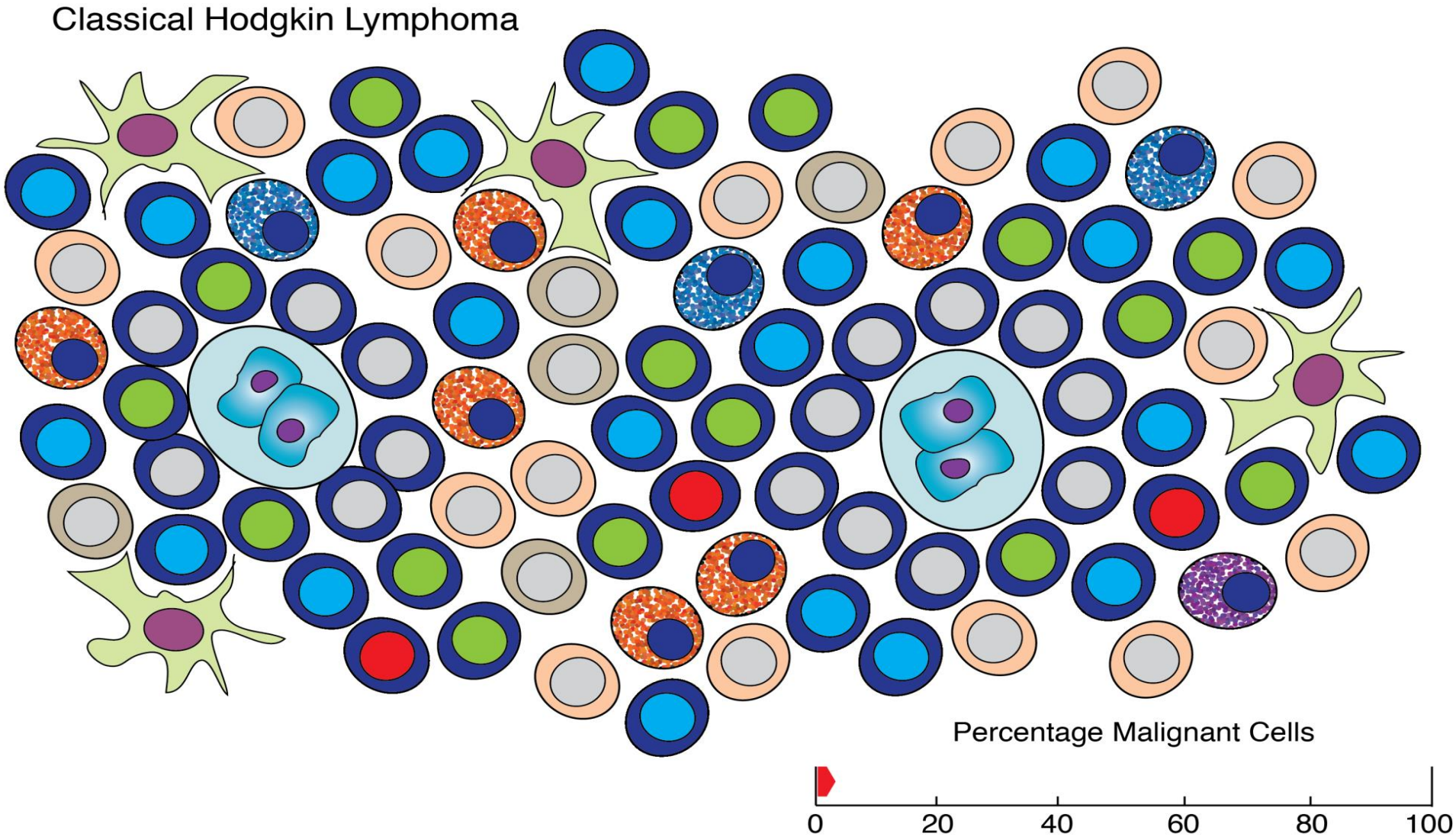
Hodgkin lymphoma -
A paradigm for the importance of the microenvironment

Dorothy Reed Mendenhall
(1874-1964)

Reed Sternberg cell



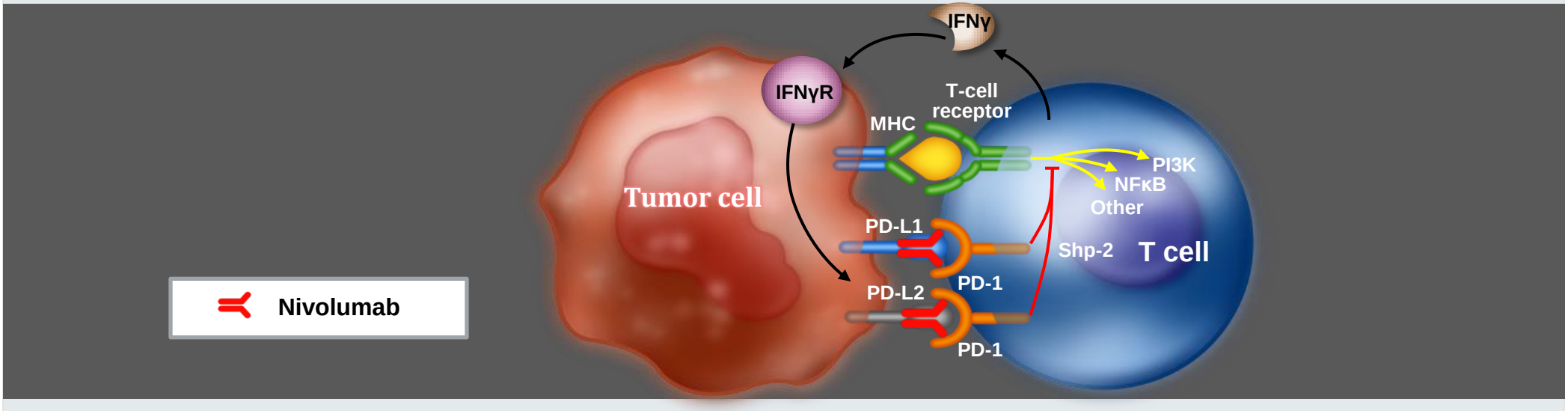
The microenvironment in classical HL is unique



David Scott and Randy Gascoyne. Nature Reviews Cancer 2014

Background

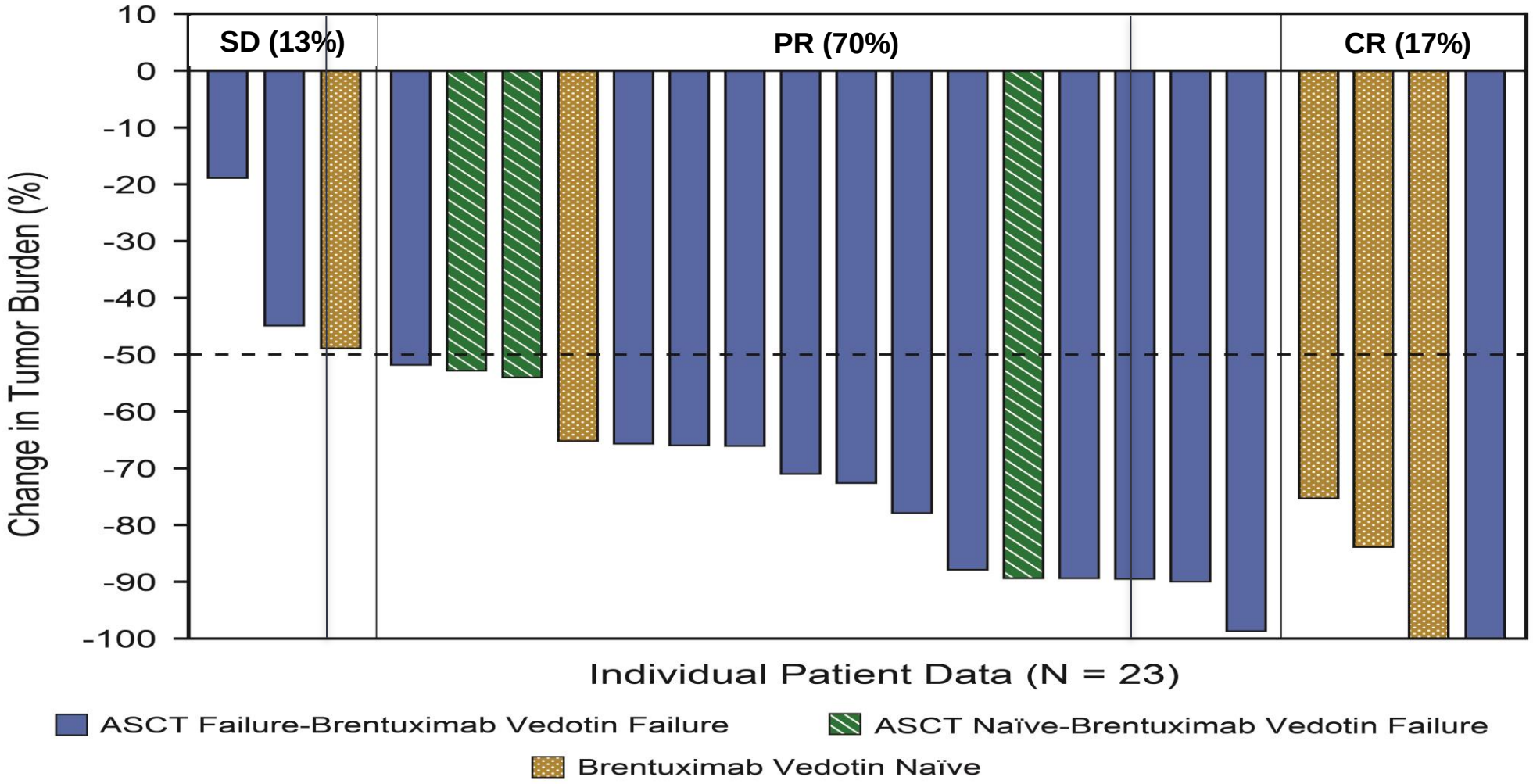
- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab is a fully human IgG4 anti-PD-1 antibody which selectively blocks the PD-1 and PD-L1/PD-L2 interaction.



- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors.

Brahmer et al N Engl J Med 2012;366:2455
Topalian et al N Engl J Med 2012;366:2443-54

Best Response



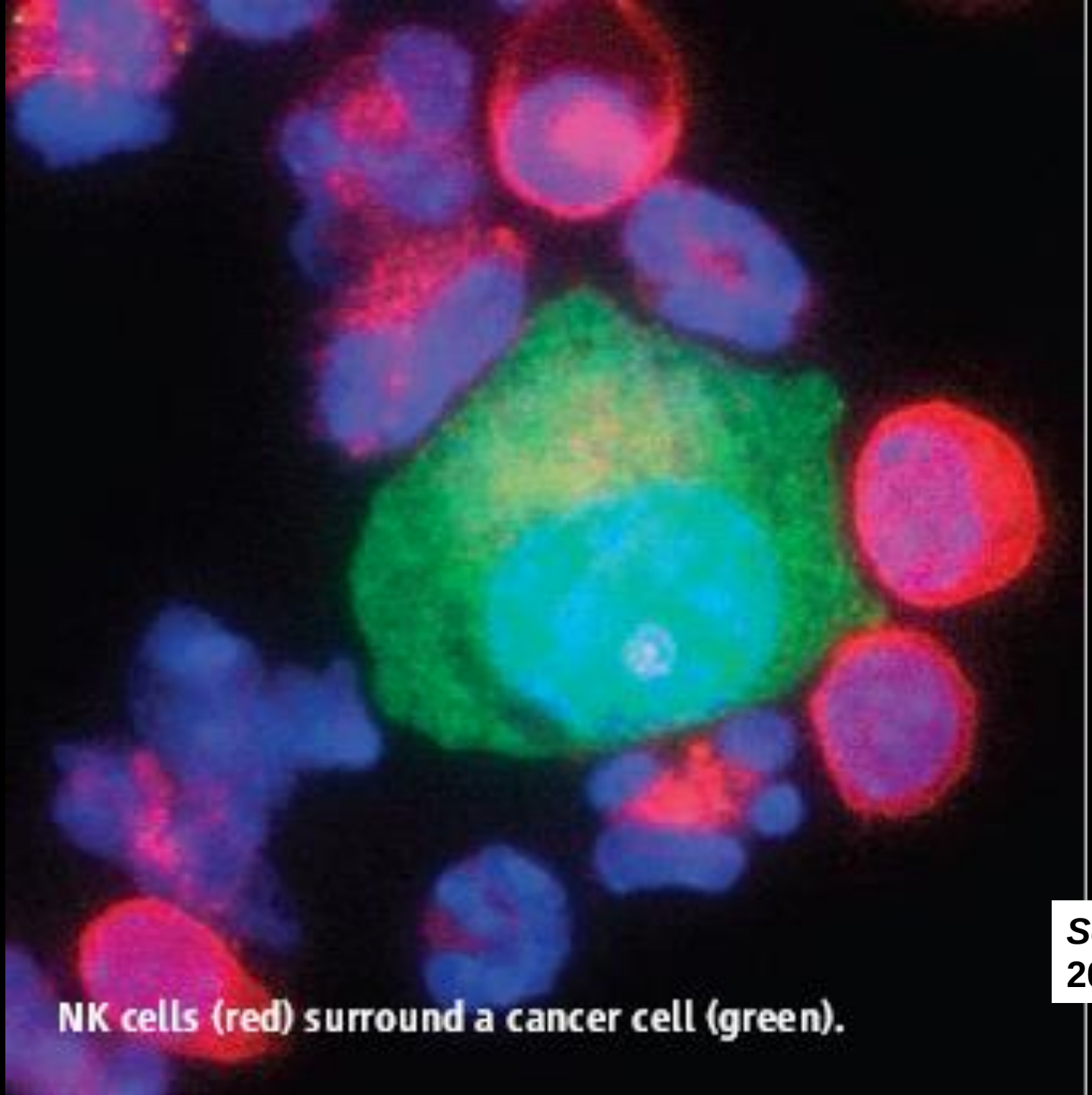
Immunotherapy with CD19-specific chimeric antigen receptor-modified T cells of defined subset composition for B cell NHL

Abstract 183

Fred Hutchinson Cancer Research Center

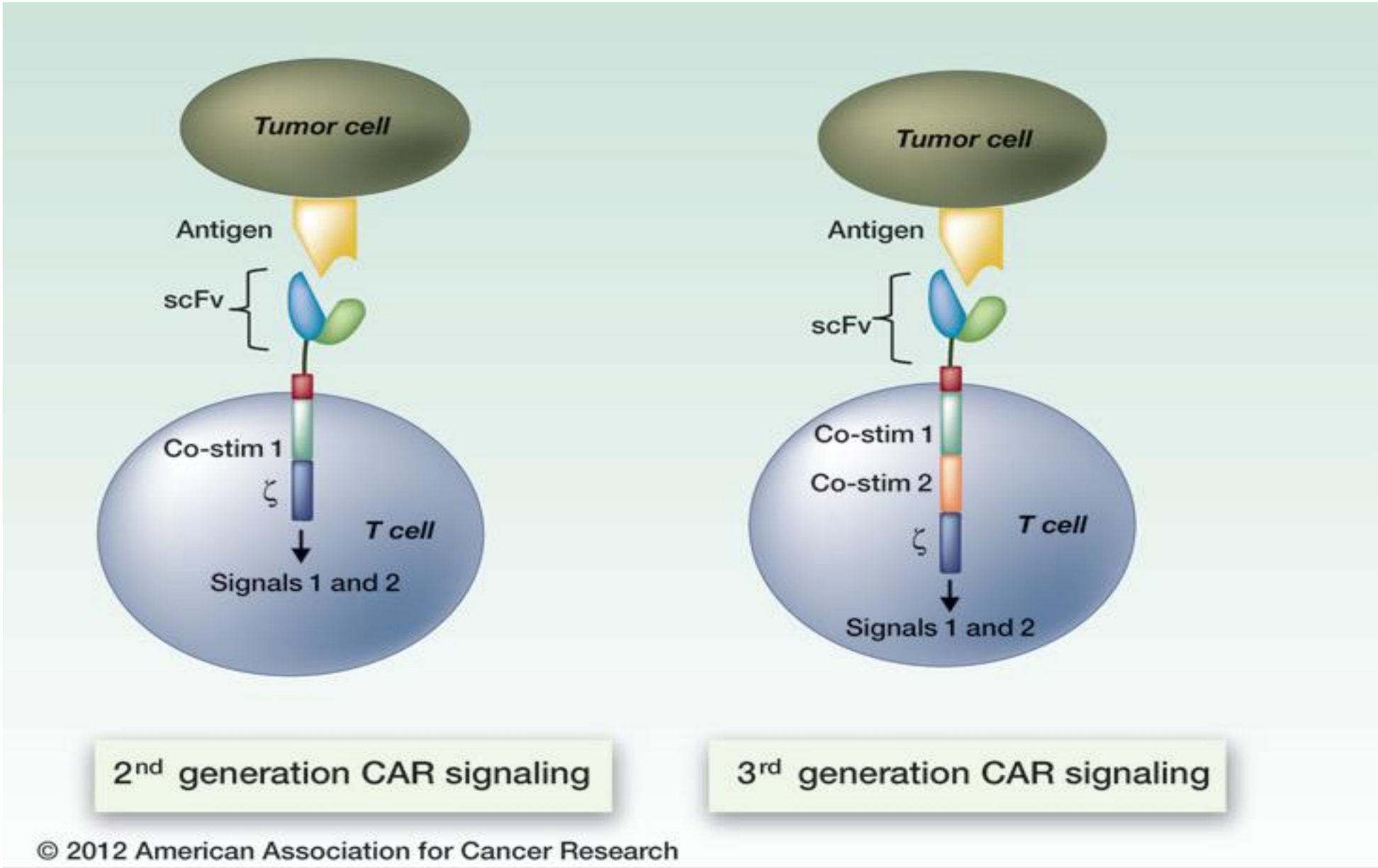
Cameron Turtle, Laila Hanafi, Carolina Berger, Ted Gooley, Tanya Budiarto, Katherine Melville, Barbara Pender, Emily Robinson, Daniel Sommermeyer, Michael Hudecek, Colette Chaney, Sindhu Sherian, Lori Soma, Xueyen Chen, Brent Wood, Daniel Li, Shelly Heimfeld, Michael Jensen, Stanley Riddell, David Maloney

Cytotoxic T-cells attacking an infected cell



NK cells (red) surround a cancer cell (green).

Science, 2006;312:974



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New Therapeutic Agents for Lymphoproliferative Neoplasms

New agents	$ / patient / course
CHOP	600
Rituximab single agent	12,000
Rituximab + chemo	24,000
Thalidomide	44,000
Alemtuzumab	36,000
Bortezomib	42,000
Brentuximab vedotin	135,000
Ibrutinib	100,000/y
CAR-T-cell immunotherapy	> 500,000

Acknowledgements

BCCF

$10M

C… …er

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Bruce Woolcock
Robert Kridel
Fong Chun Chan
Suman Singh
Holly Eely
Arla Yost

$9M

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L'Institut de recherche Terry Fox

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Jacquie Schein
Richard Moore
Karen Mungall
Inanc Birol
Martin Krzywinski
Greg Morin
Robyn Roscoe
Armelle Troussard

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Sam Aparicio
Damian Yap

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The clinicians & patients of BC

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