Dr. C. Tom Kouroukis

New and upcoming treatments for Lymphoma

Hamilton
Living Well with Lymphoma

New and upcoming treatments for Lymphoma

Dr. Tom Kouroukis

Hamilton Convention Centre

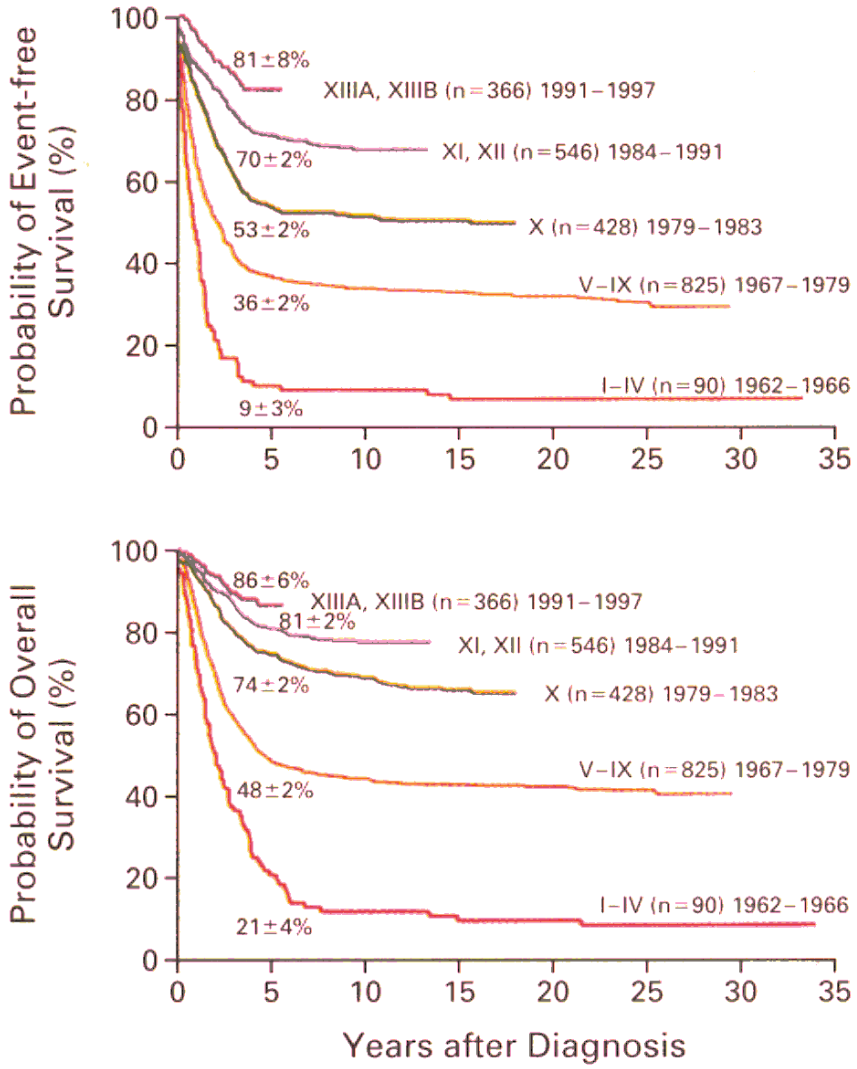
November 23, 2013

Overview

- Importance and design of clinical trials
- Drug development
- Principles of traditional chemotherapy
- New agents
  - Chemotherapy (Bendamustine)
  - Antibodies (Immunotherapy)
    - GA101 (Obinutuzumab)
    - Brentuximab (Adcetris)
  - BTK (Bruton's Tyrosine Kinase) Inhibitors (Ibrutinib)
  - New uses for existing drugs
    - Lenalidomide (Revlimid)

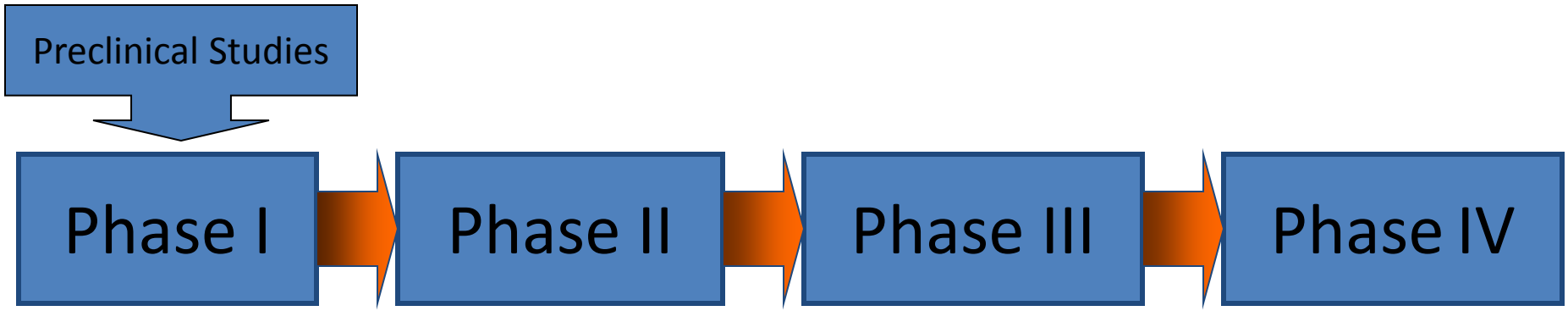
Importance of Clinical Trials

Example from childhood leukemia (ALL)



New England Journal of Medicine

Importance of Clinical Trials



- Few patients
- What's the highest/best dose that we can achieve
- Outcome: Toxicities

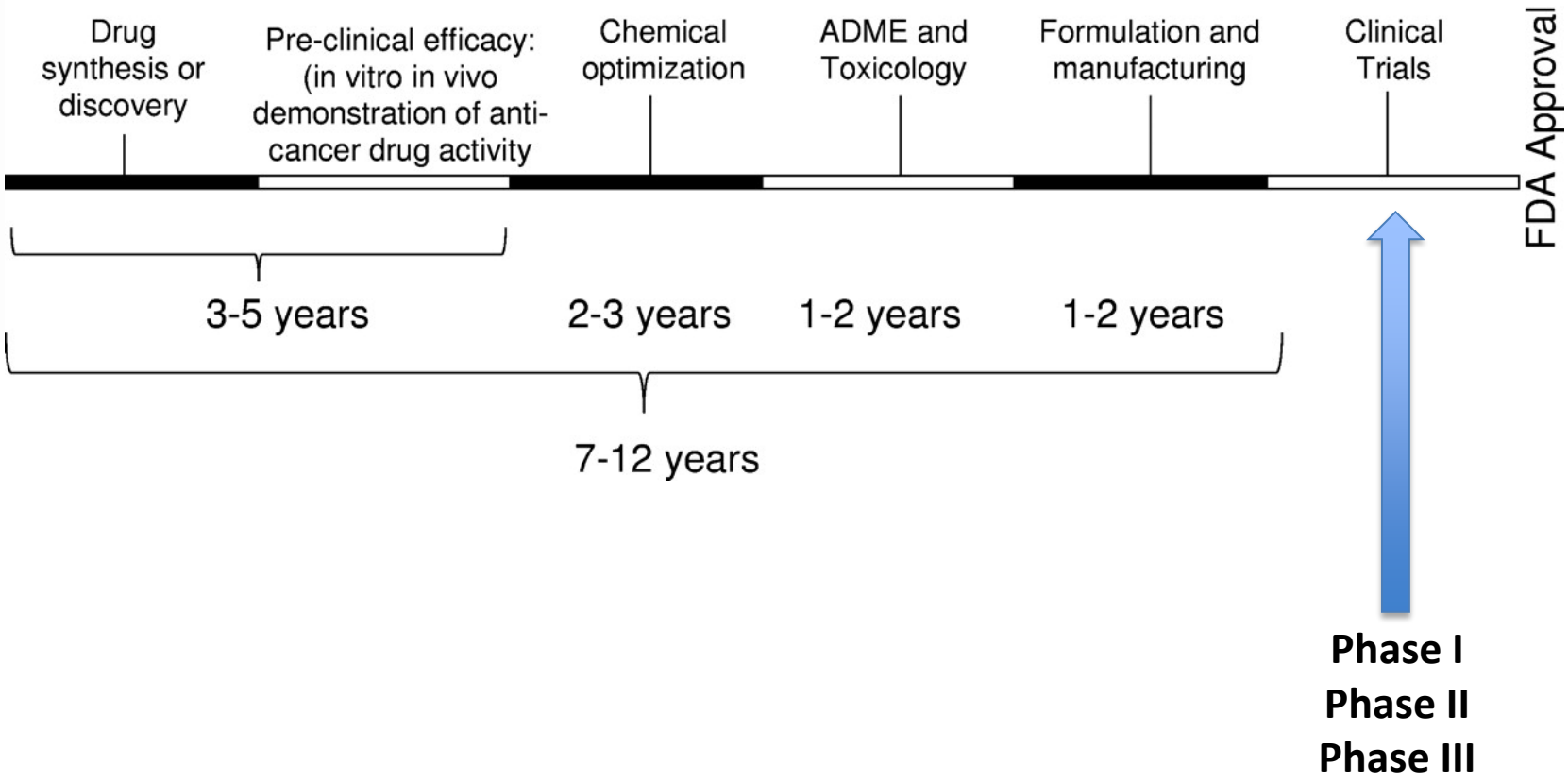
- Slightly more patients
- What's the effect at the best dose
- Outcomes: Efficacy & Toxicity

- Large number of patients
- Comparative trial – 2 or more treatments
- Outcomes: Survival, disease control

- Post marketing surveillance
- Huge numbers
- Outcomes: Unusual toxicities

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

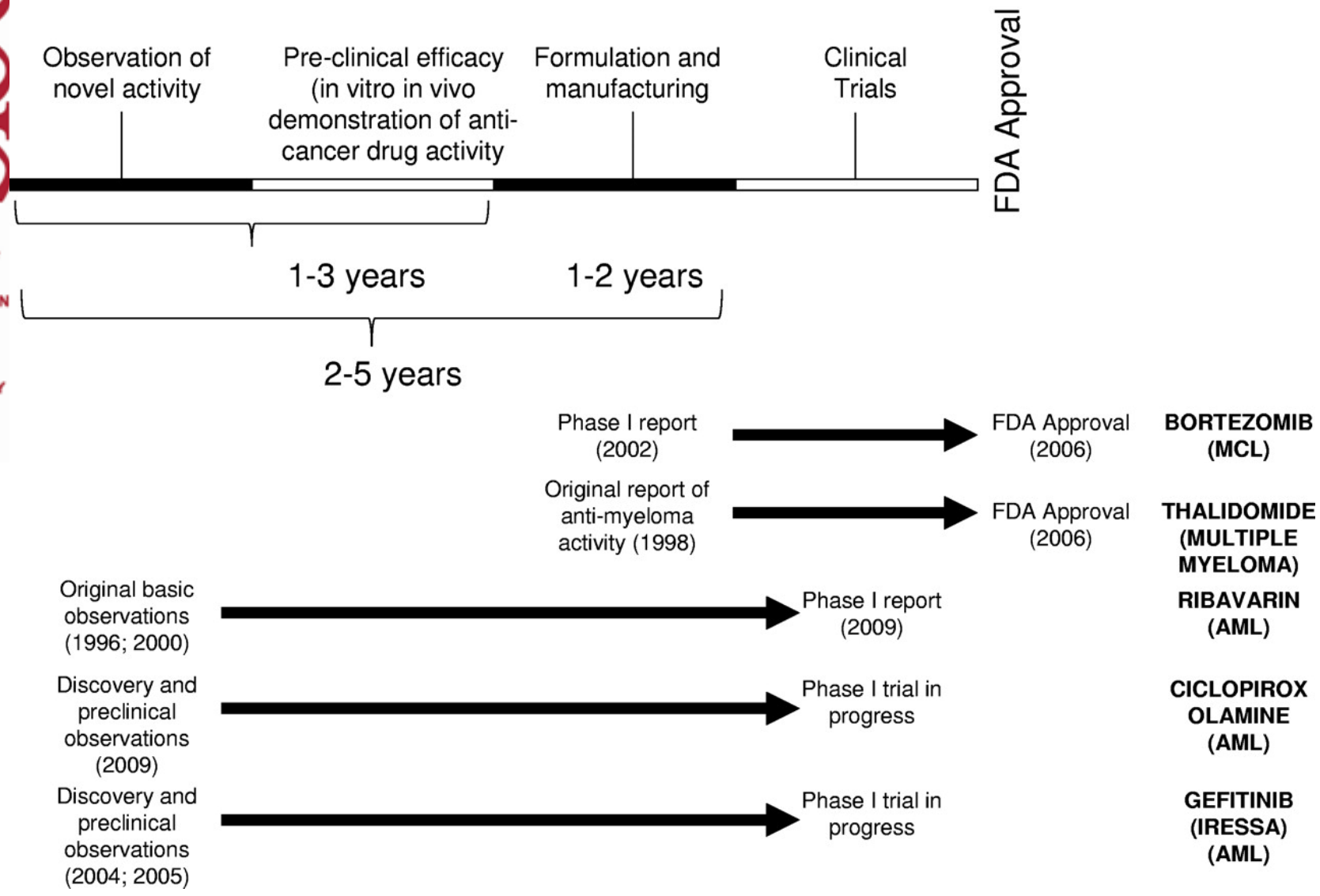
Time line for NEW drug discovery



Sukhai M A et al. Blood 2011;117:6747-6755

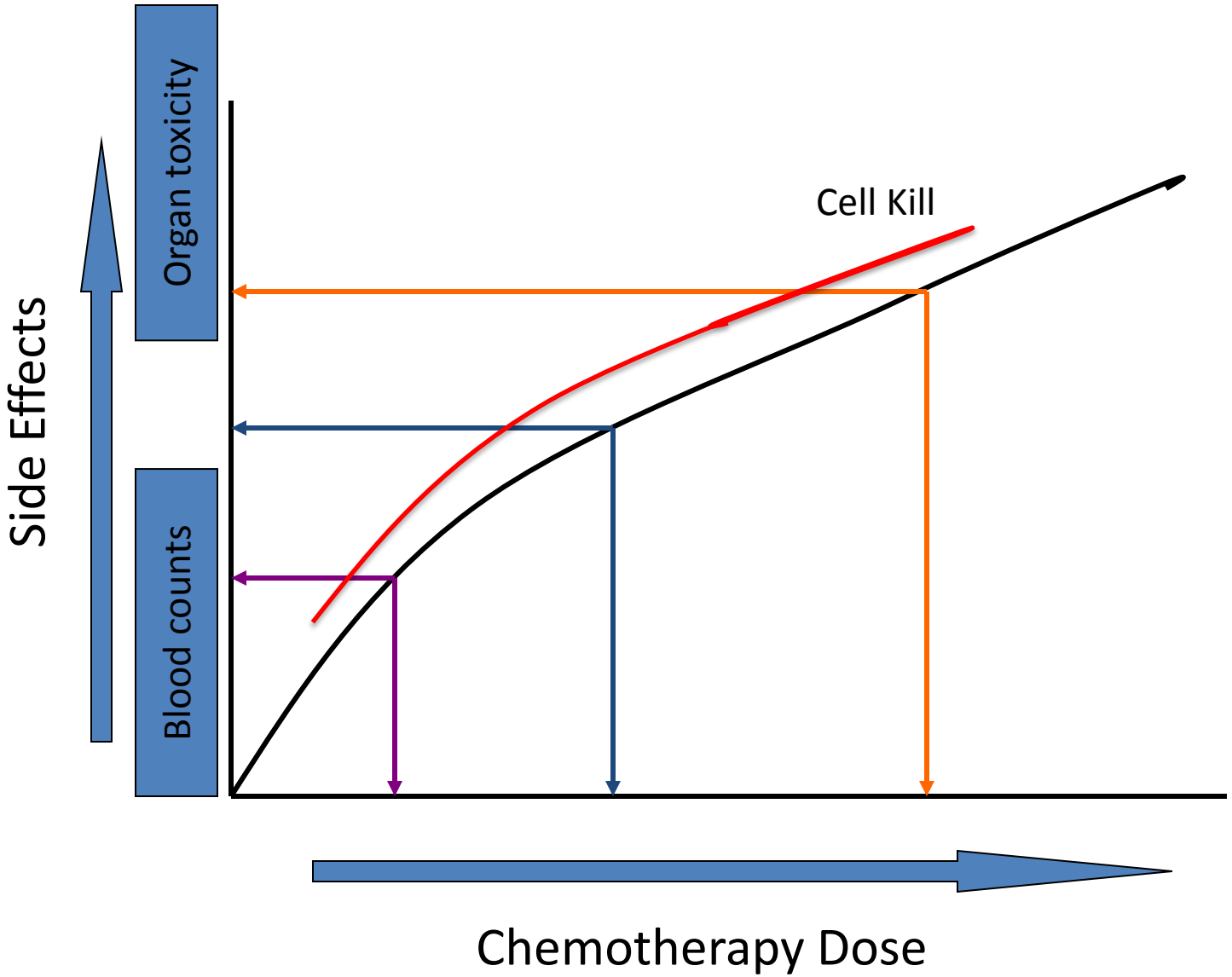
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Time line for drug repurposing

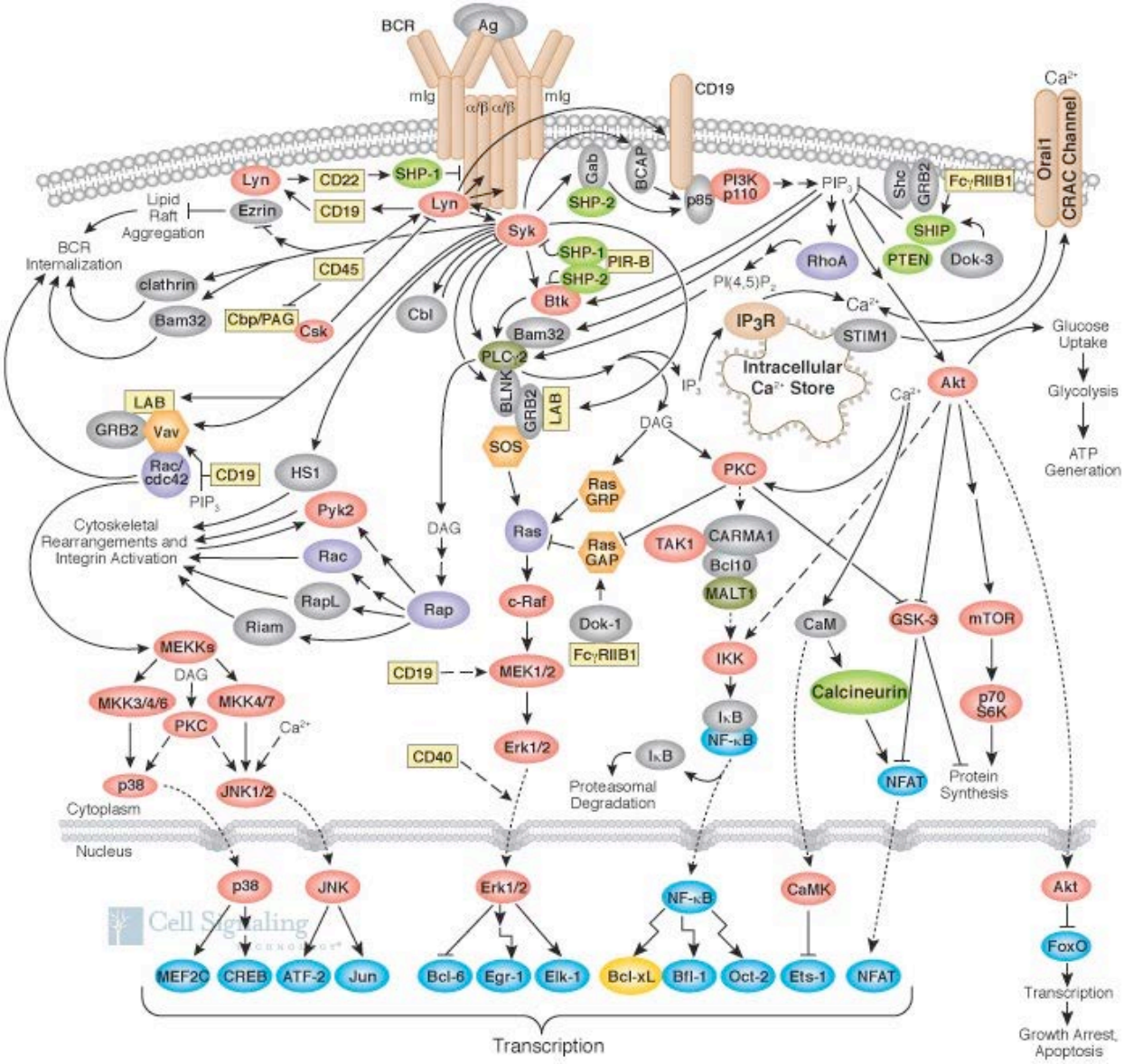


Sukhai M A et al. Blood 2011;117:6747-6755

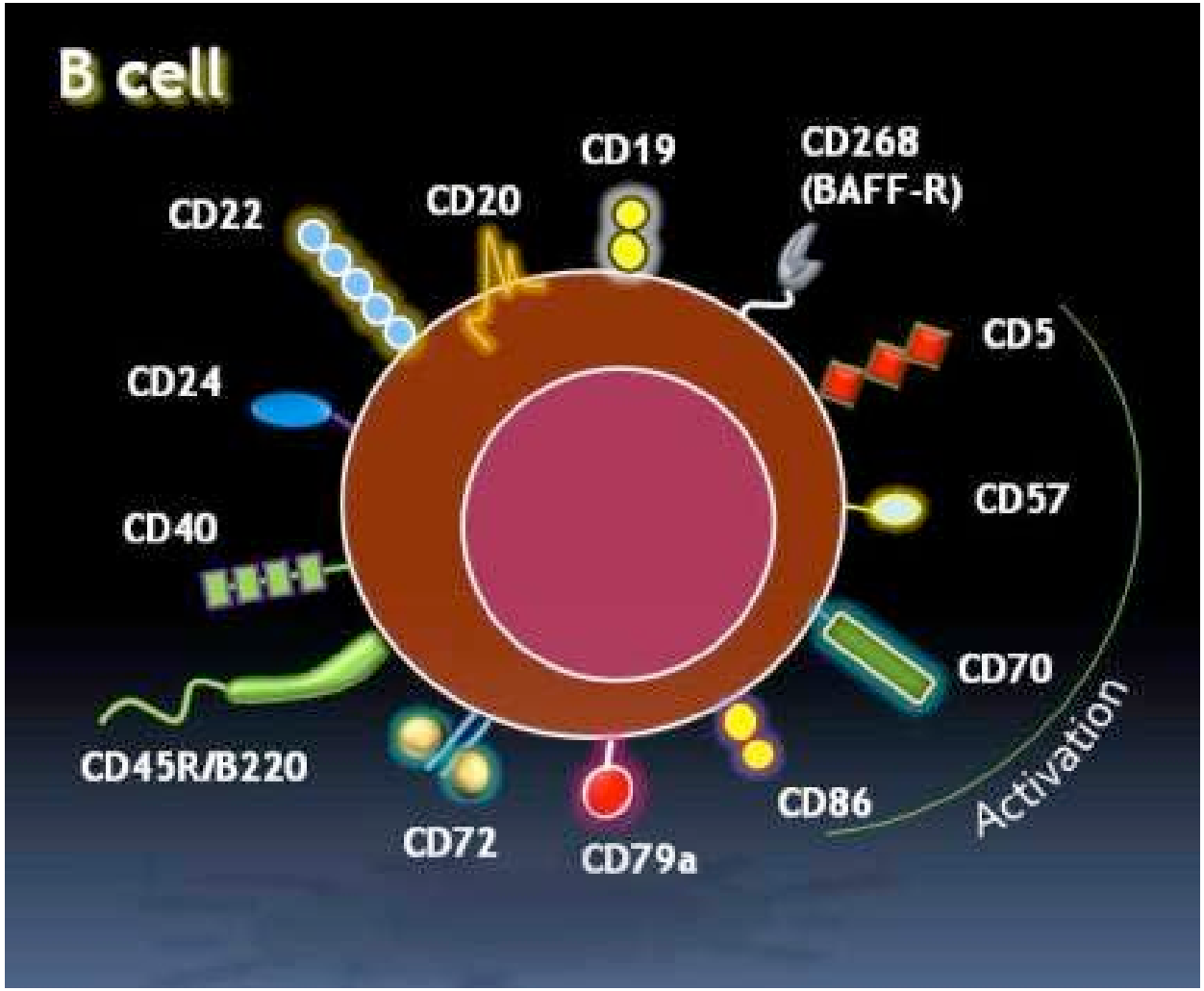
Principles of Chemotherapy



What to target?



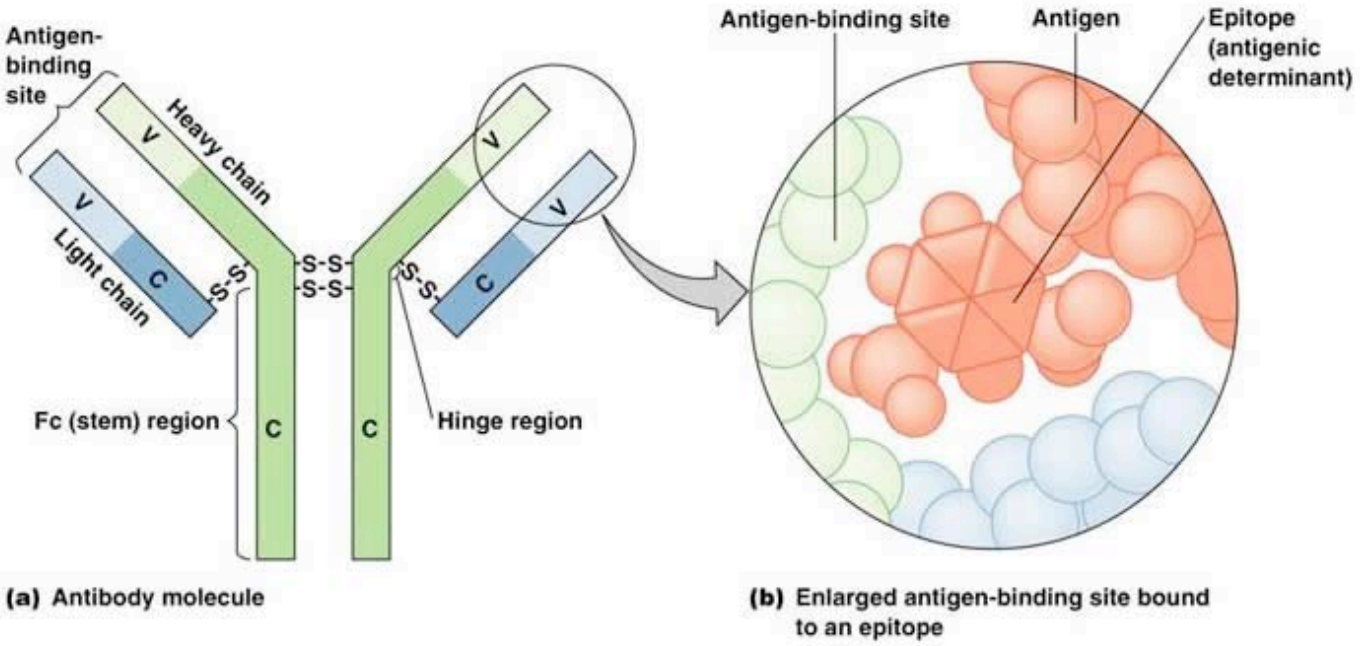
Potential cell surface targets



Antibodies

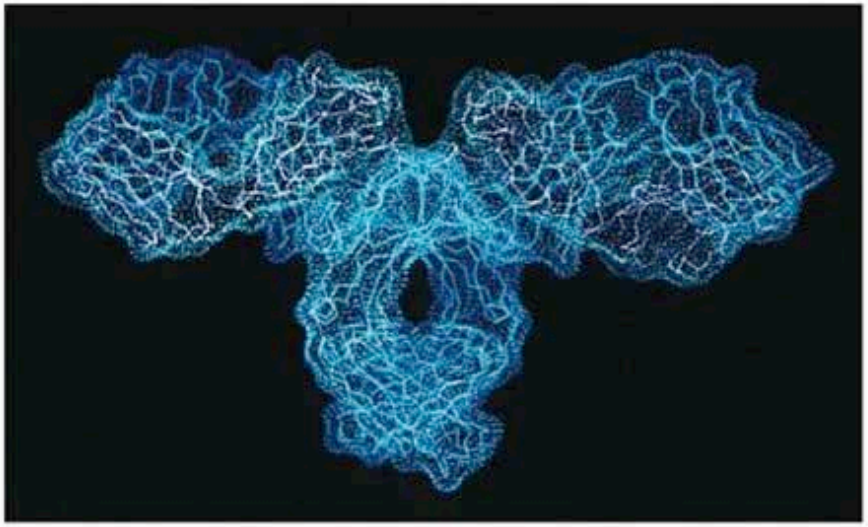
Mimicking the human immune system

Antibodies



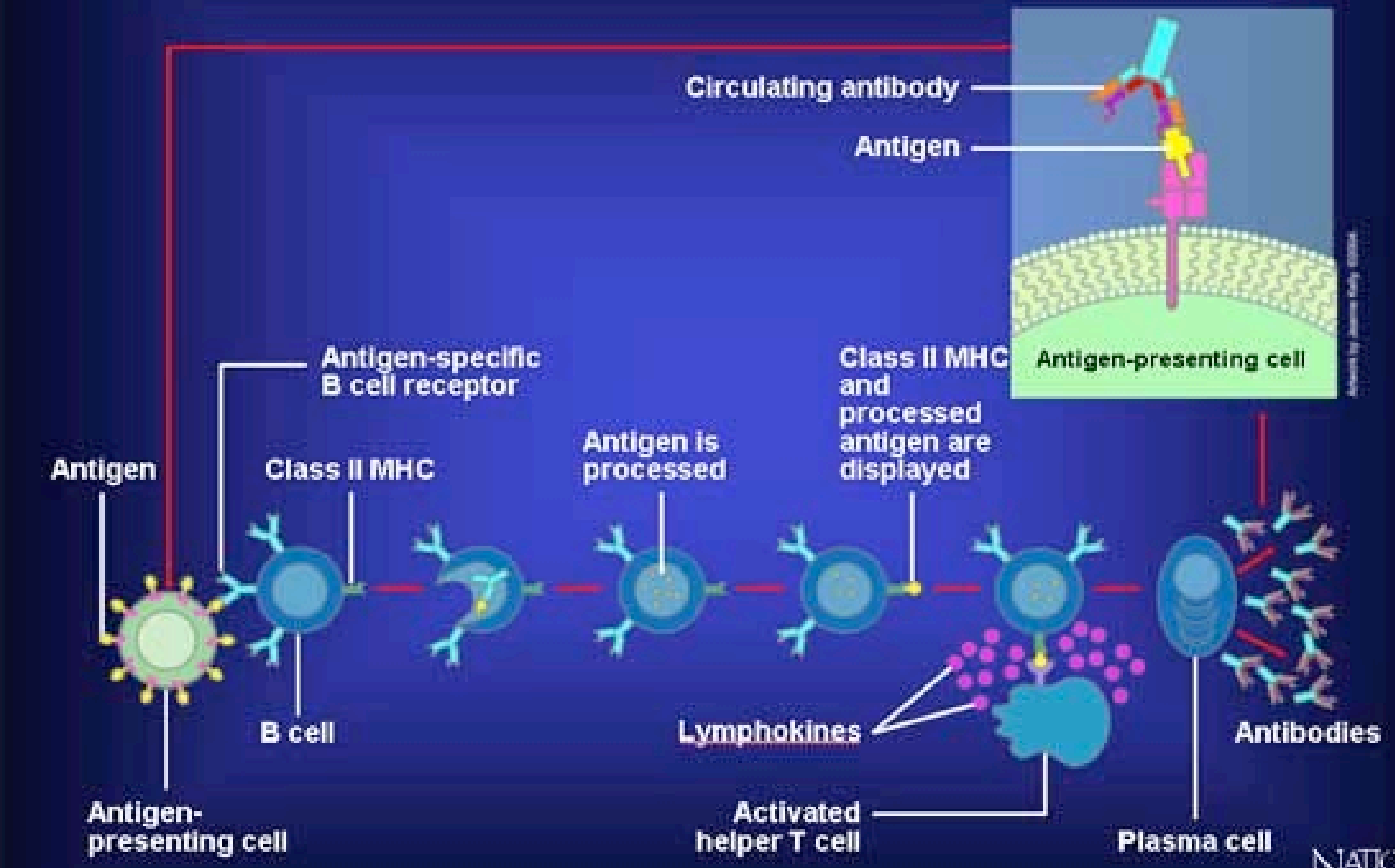
(a) Antibody molecule

(b) Enlarged antigen-binding site bound to an epitope

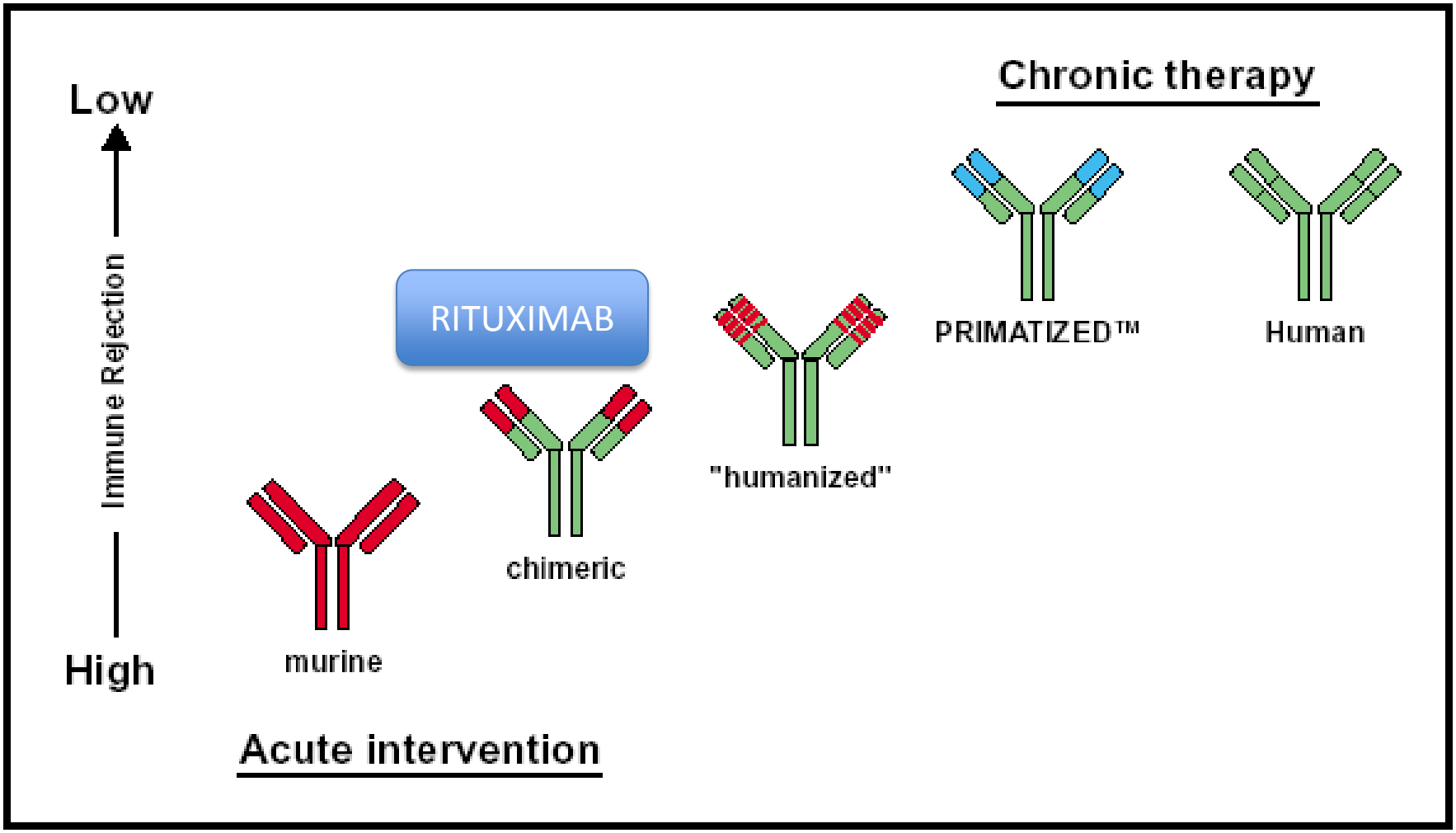


(c) Computer graphic model of an antibody molecule

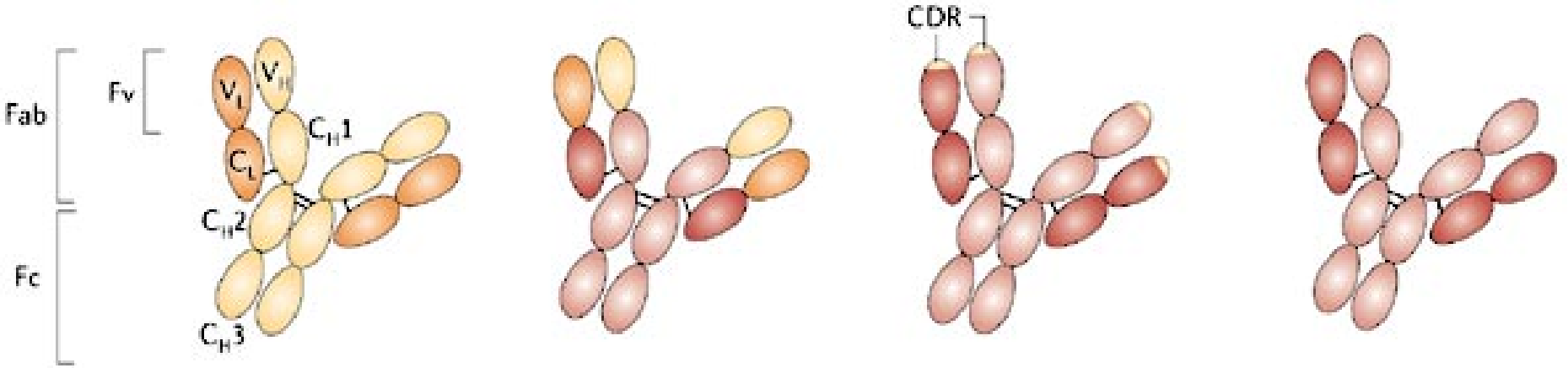
Activation of B Cells to Make Antibody



Generations of antibody technology



Reff et al., Cancer Control, 2002



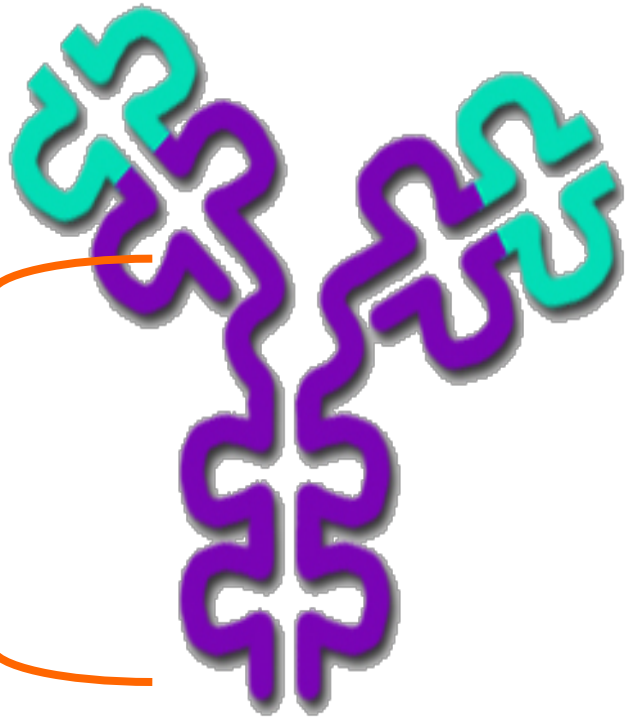
Type of mAb	Murine	Chimeric	Humanized	Human
	Ibritumomab tiuxetan (CD20); IgG1κ*	Cetuximab (EGFR); IgG1κ	Trastuzumab (ERBB2); IgG1κ	Panitumumab (EGFR); IgG2
	Tositumomab-I^{131} (CD20); IgG2aλ*	Rituximab (CD20); IgG1κ	Bevacizumab (VEGF); IgG1	
			Alemtuzumab (CD52); IgG1κ	
			Gemtuzumab ozogamicin (CD33); IgG4κ*	

Imai and Takaoka *Nature Reviews Cancer* **6**, 714–727 (September 2006) | doi:10.1038/nrc1913

nature REVIEWS CANCER

Rituximab

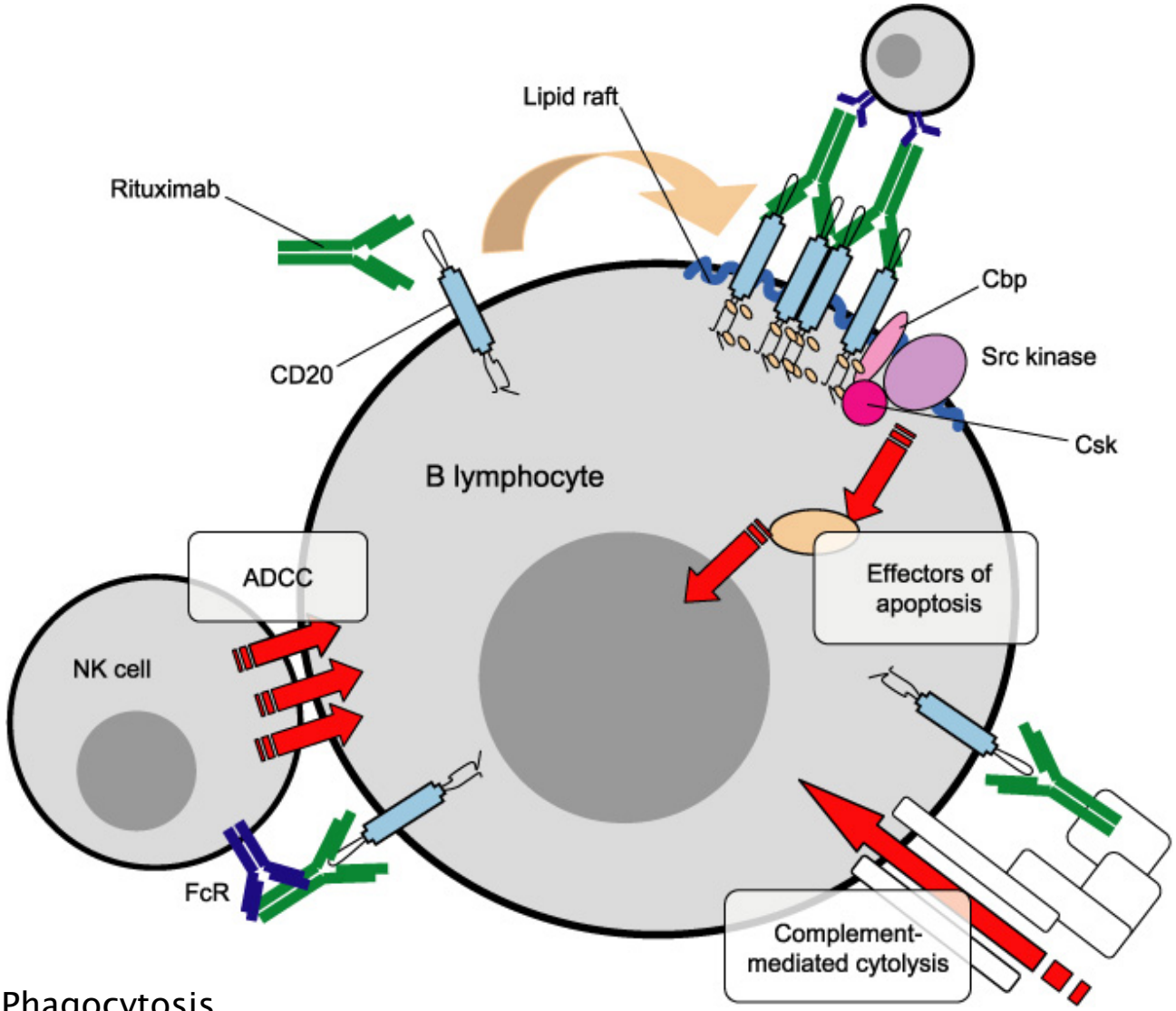
Human/Murine Chimeric Antibody



Variable region is from the anti-CD20 murine antibody fragment IDEC-2B8

Human IgG1 Fc domain and *k*-constant regions

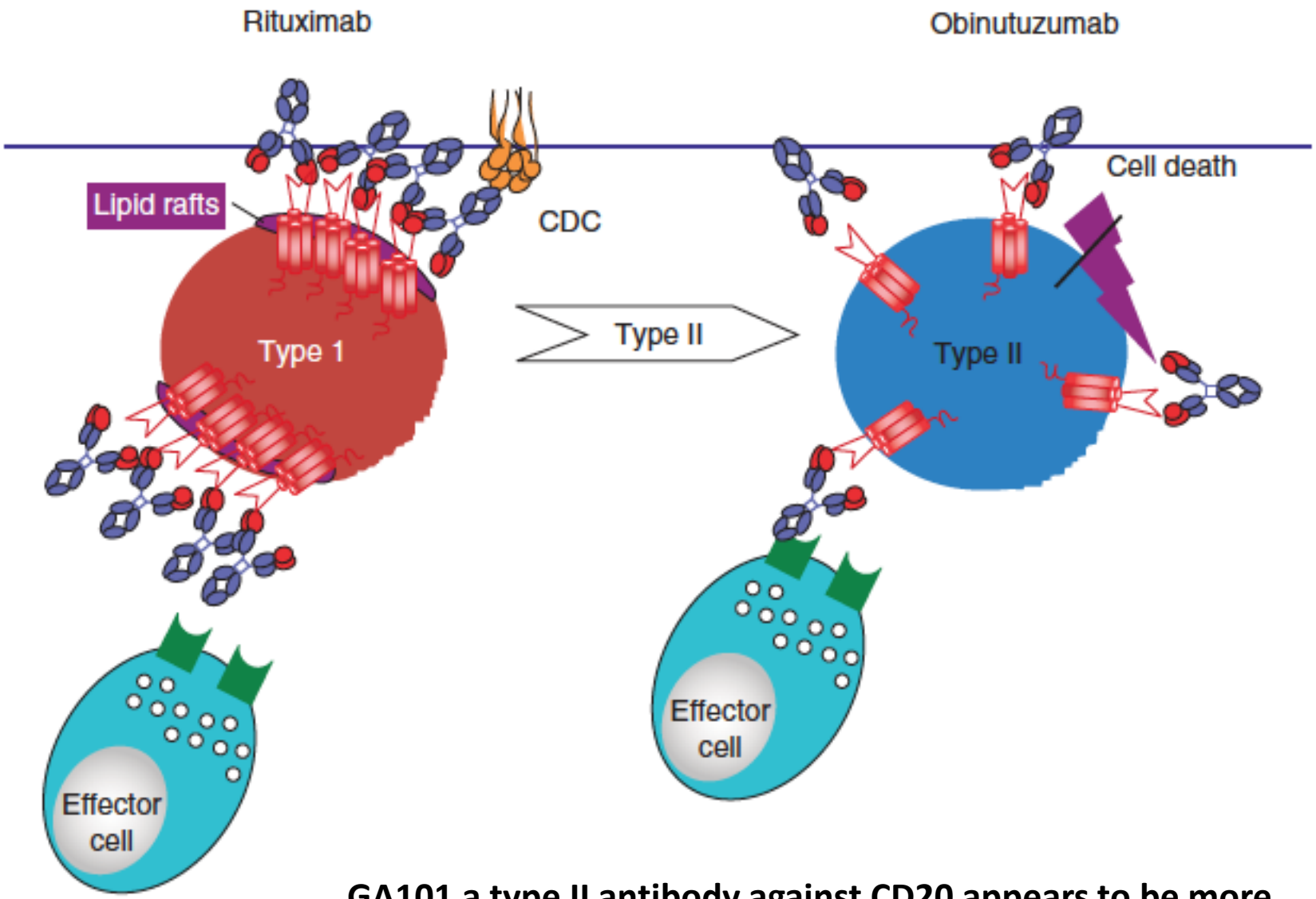
Proposed Mechanisms of Action



Phagocytosis
Monocyte/macrophage

Smith MR, Oncogene 2003;22:7359-7368

GA101



GA101 a type II antibody against CD20 appears to be more effective than Rituximab

Brentuximab

Antibody with a “punch”

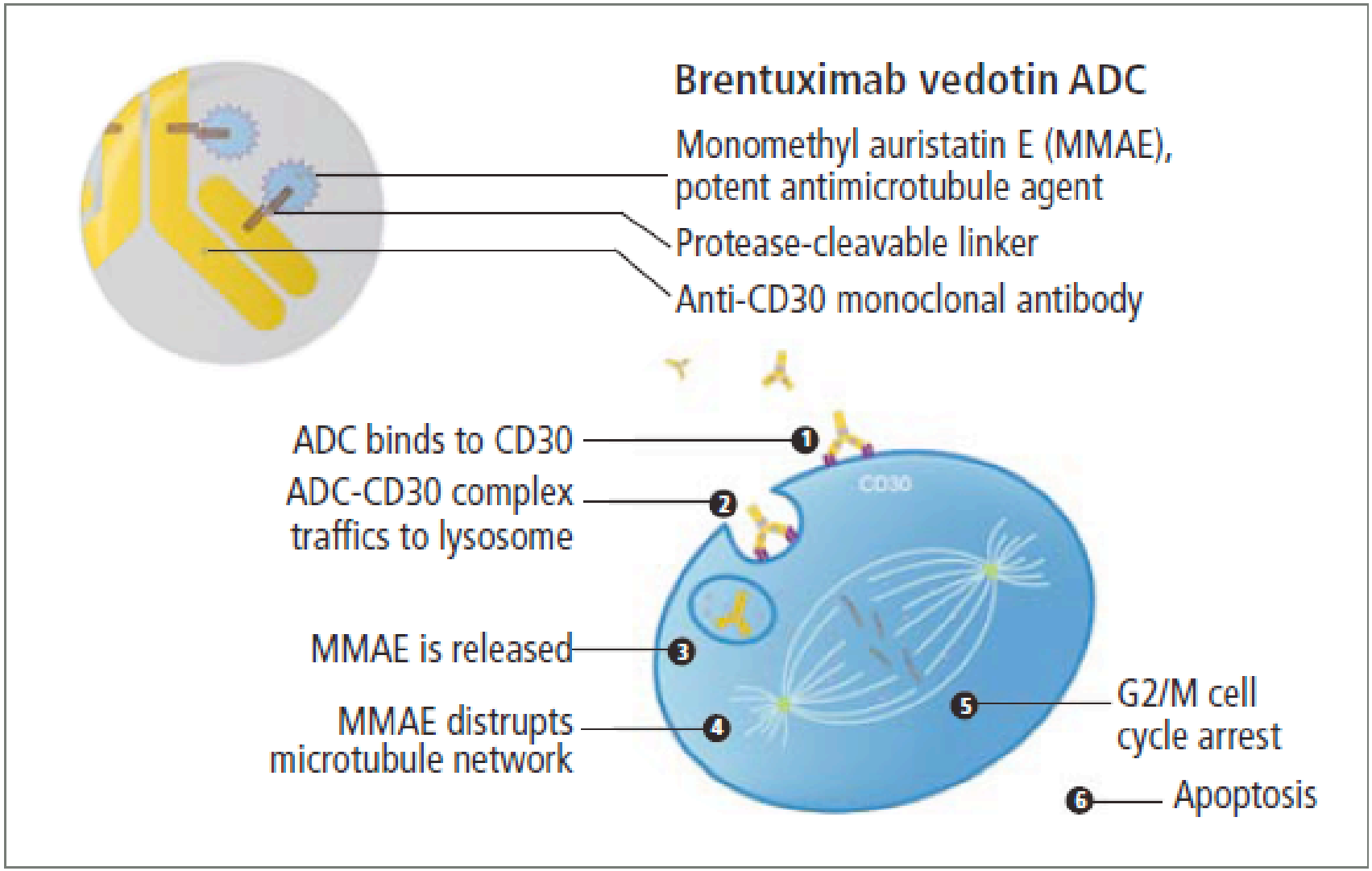
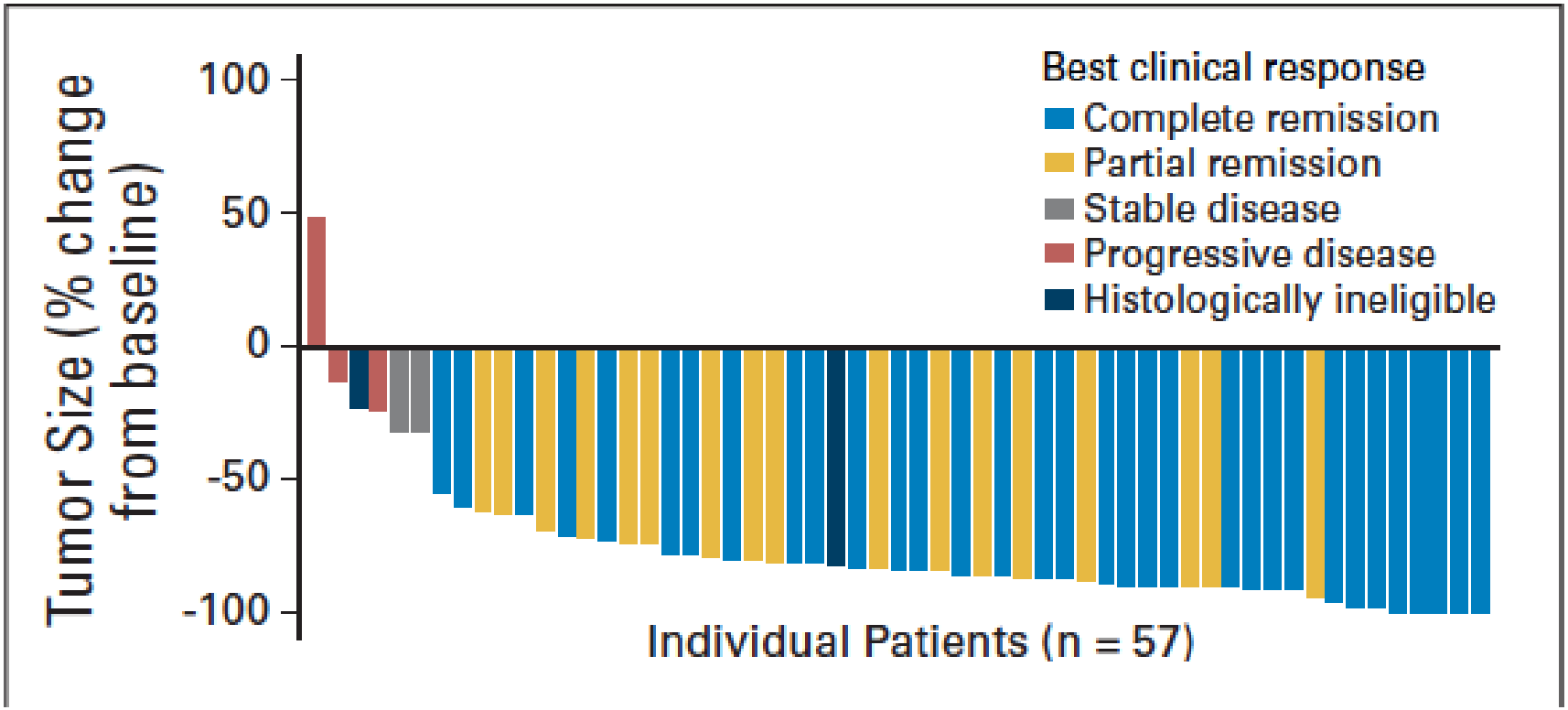


Figure 1. Brentuximab Vedotin Structure and Mechanism of Action[15]

Brentuximab in recurrent anaplastic large cell lymphoma

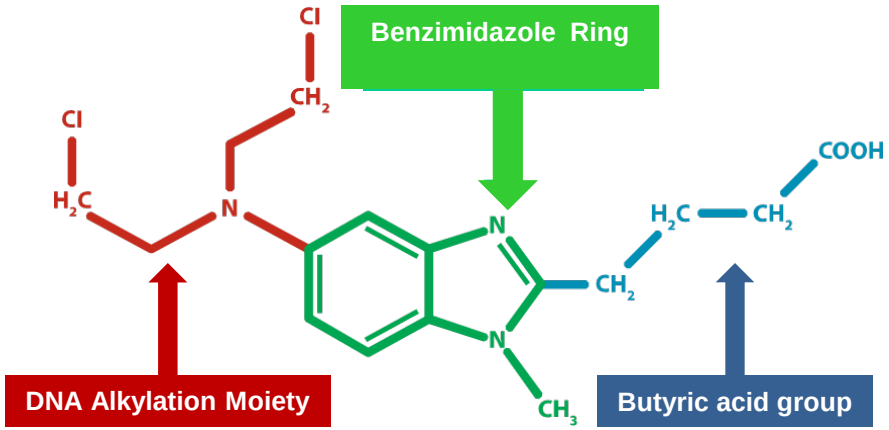


Pro et al., J Clin Oncol, 2012

Bendamustine

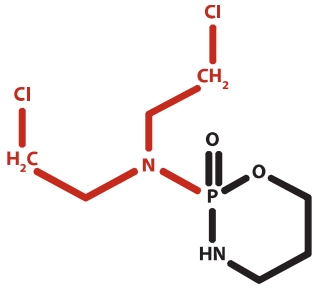
Rediscovering an older chemotherapeutic drug

Bendamustine

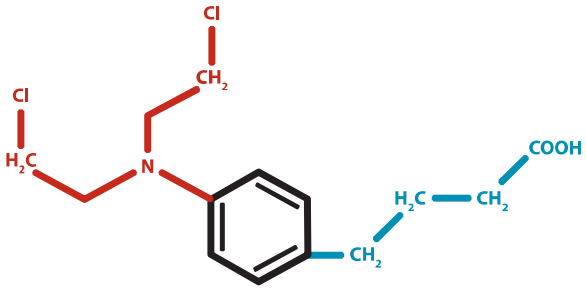


- Developed in the 60's in former East Germany
- An alkylating molecule with unique properties:
  - Bifunctional alkylator group (2-chloroethylamine group)
  - Benzimidazole ring

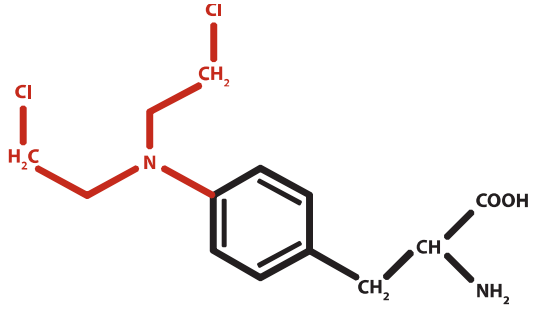
cyclophosphamide



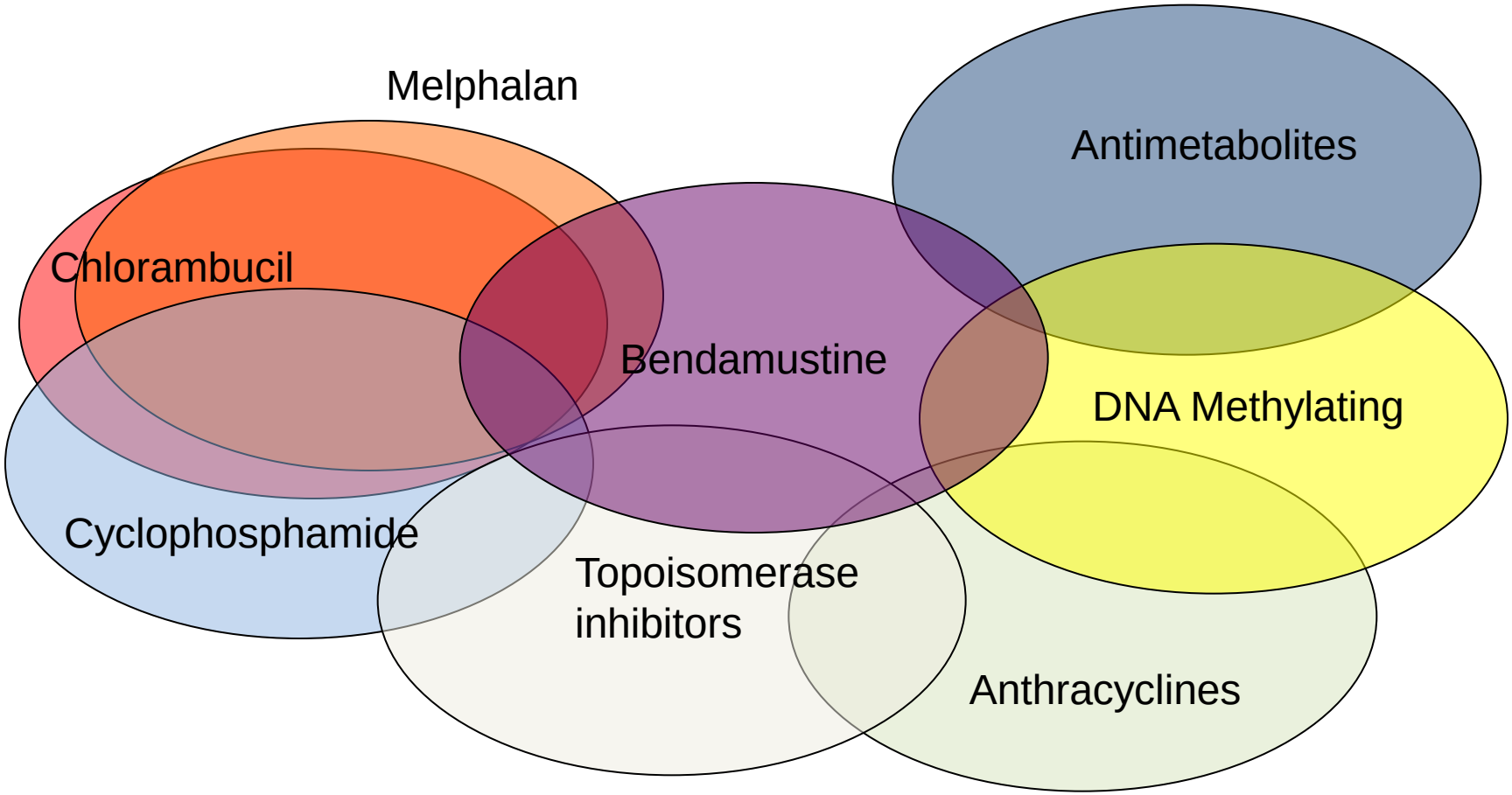
chlorambucil



melphalan



Bendamustine Lacks Cross-Correlation with other Cytotoxic Agents in NCI Compare Analysis



Leoni M.L. *et al.,* Clin Cancer Res 2008; 14(1): 309-317.

Bendamustine

- Has become part of standard therapy for follicular/mantle/indolent lymphoma along with rituximab (funded)
- Also has activity in CLL (first line)
- Given IV daily x 2 days every month for 6 months
- Being tested in other types of lymphoma (T cell, aggressive, Hodgkin's)

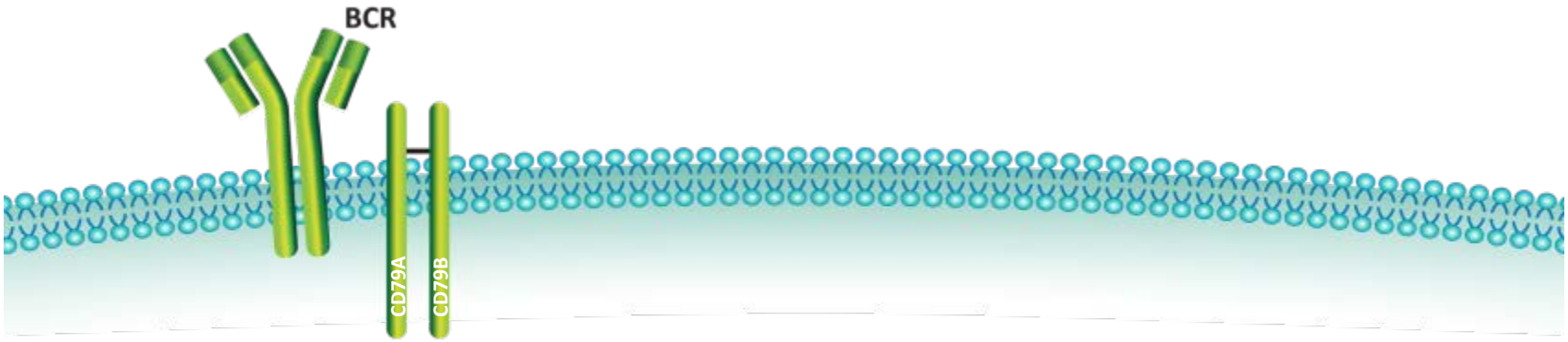
BTK inhibitors

Interrupting a key pathway inside the B cell

Ibrutinib

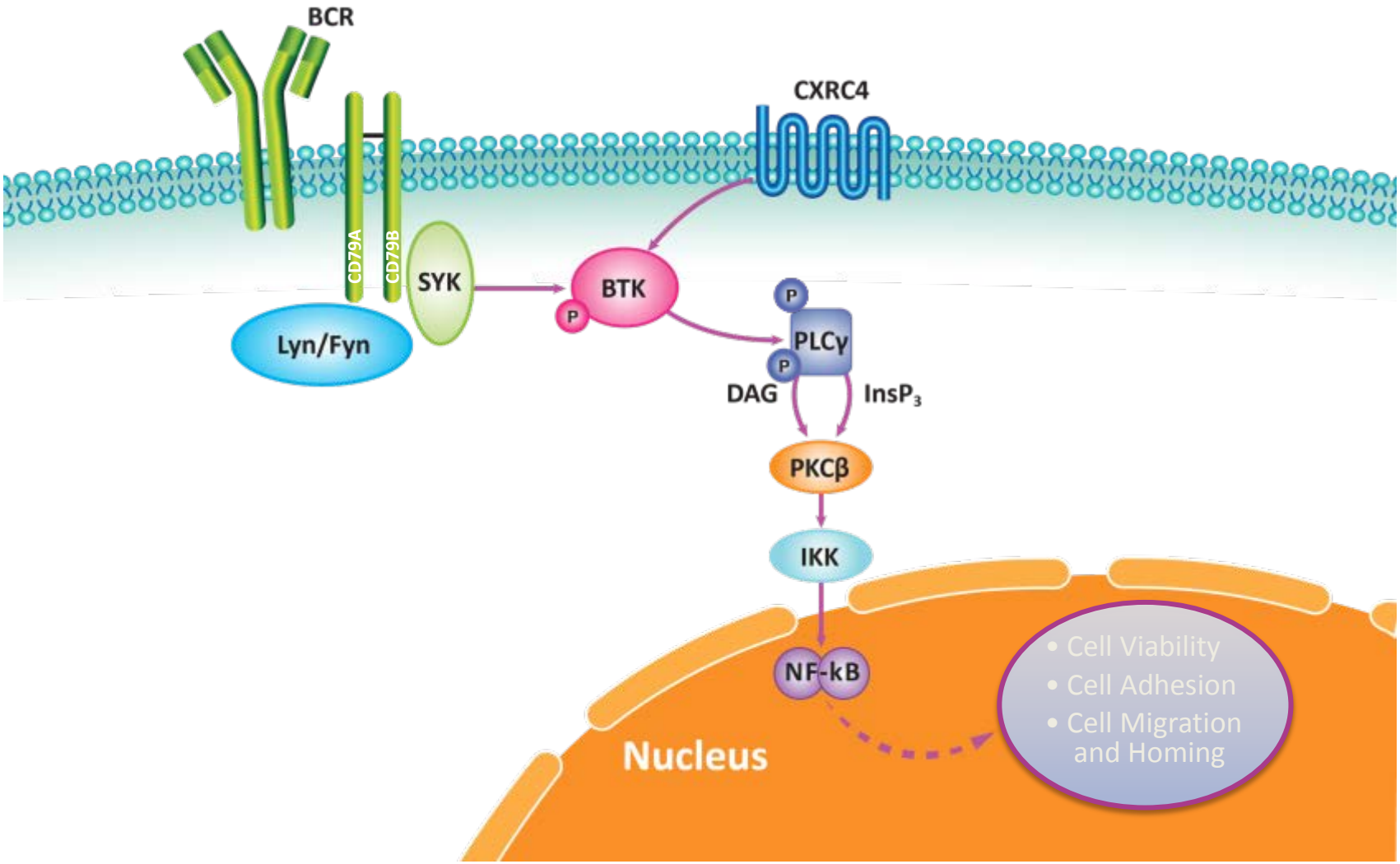
- First in class, potent, irreversible BTK inhibitor
- B cell receptor signaling pathway appears important in many B lymphoproliferative disorders
- Has been testing in CLL, Mantle cell lymphoma, follicular (low grade) lymphoma
- FDA approval for Mantle cell recently
- Many clinical trials in combination with other drugs

B-Cell Receptor (BCR): Signaling Promotes Proliferation, Differentiation, and Survival

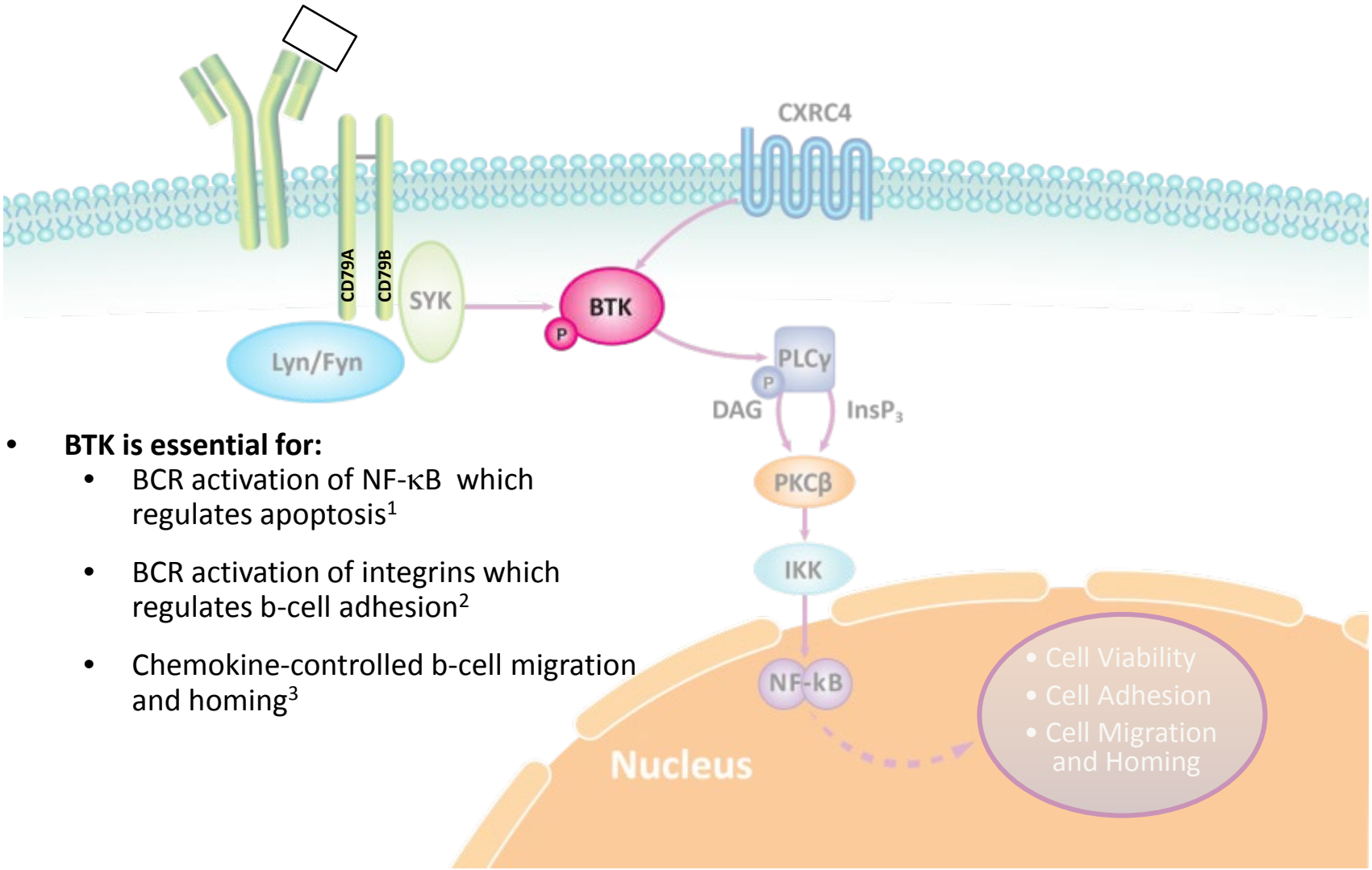


- Each B-cell expresses a unique B-cell receptor that specifically binds to its cognate antigen
- BCR is required for B-cell survival and differentiation at several stages of B-cell development from the pre-B cell stage and onwards

Bruton's Tyrosine Kinase (BTK): Signaling Pathway

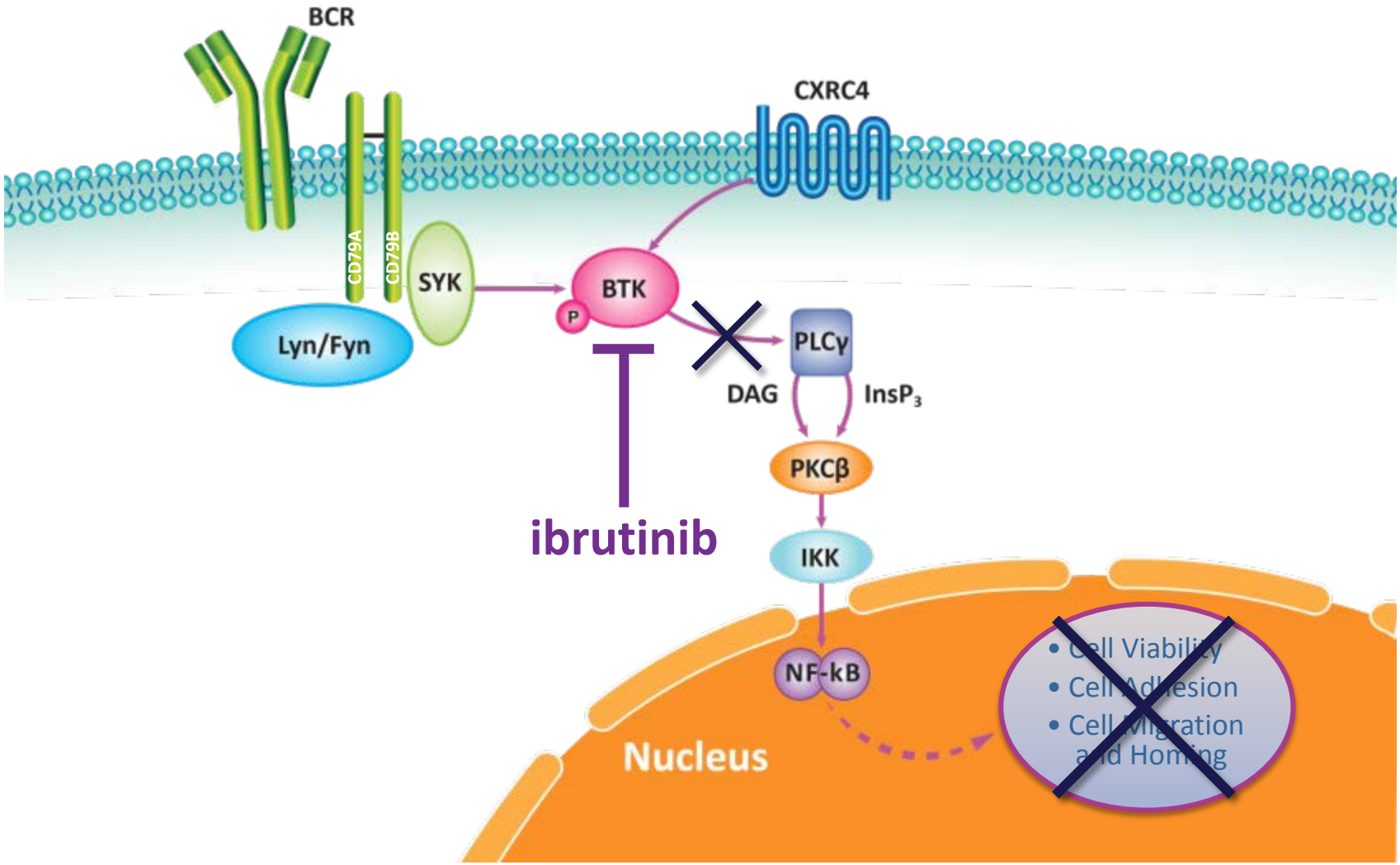


Bruton's Tyrosine Kinase (BTK): An Essential Component of the B-Cell Signaling Pathway



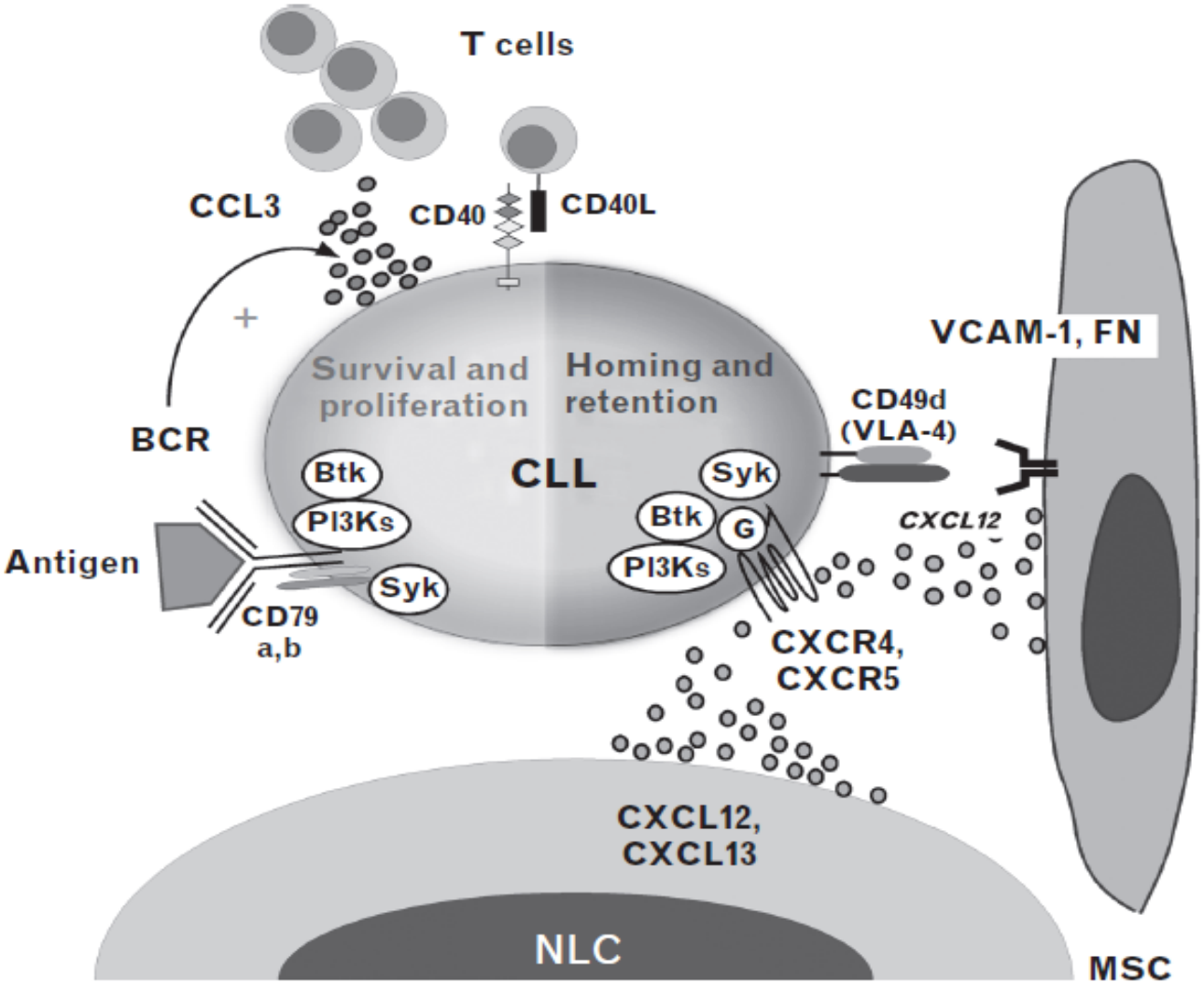
- **BTK is essential for:**
  - BCR activation of NF-κB which regulates apoptosis[1]
  - BCR activation of integrins which regulates b-cell adhesion[2]
  - Chemokine-controlled b-cell migration and homing[3]

Proposed Mechanism of Action in CLL & MCL: Ibrutinib Blocks Malignant B-Cell Growth and Proliferation



Buggy JJ and Elias L. *Int Reviews of Immunology*. 2012; 31:119-13.

Don’t forget about the neighbourhood



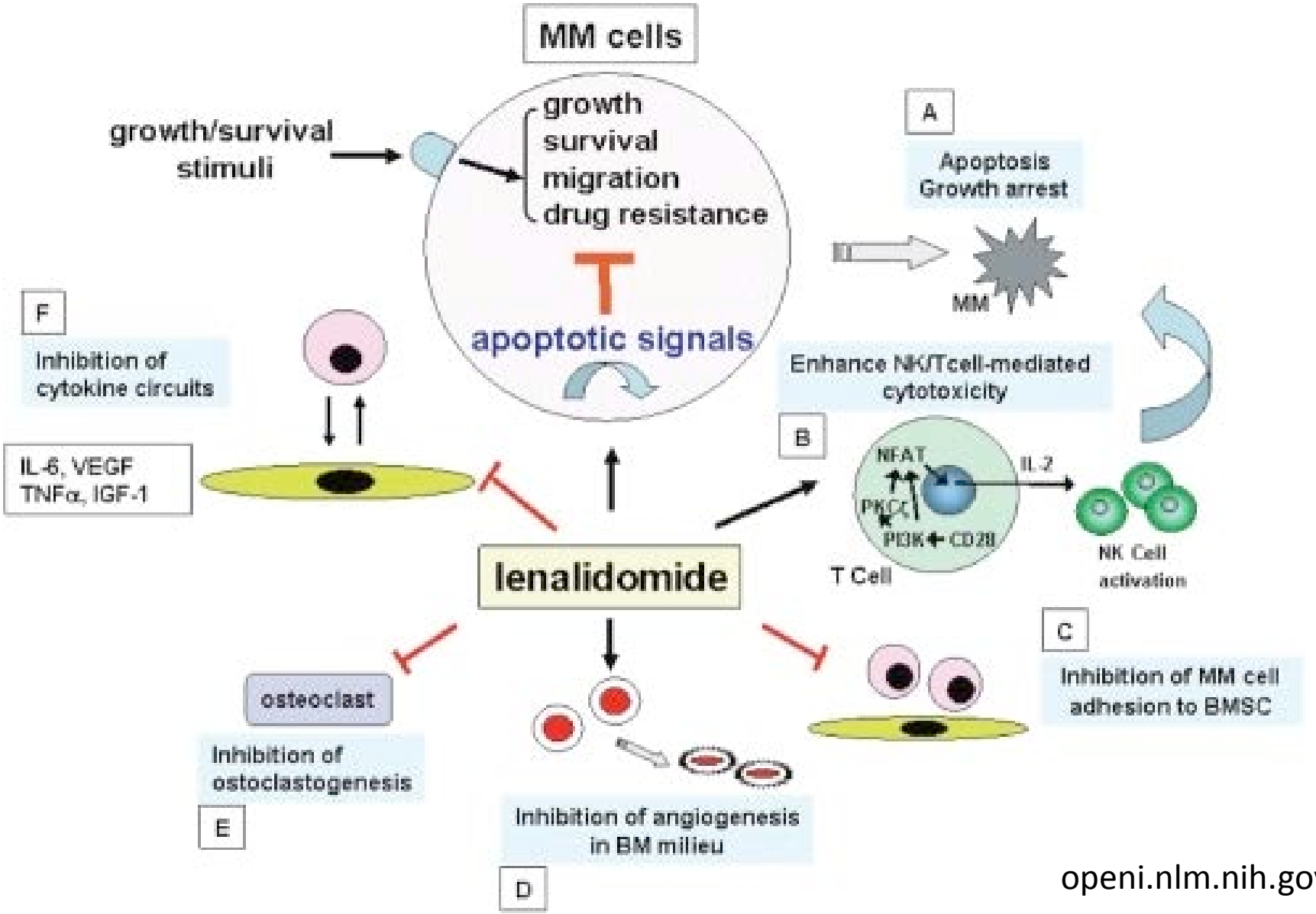
Lenalidomide

Repurposing a drug for something else

Lenalidomide

- Widely used to treat another blood cancer, multiple myeloma
- It is a newer, more potent version of thalidomide
- Used with steroids, and often combined with other drugs in myeloma
- Good side effect profile means that it can be taken for years

Many mechanisms of action

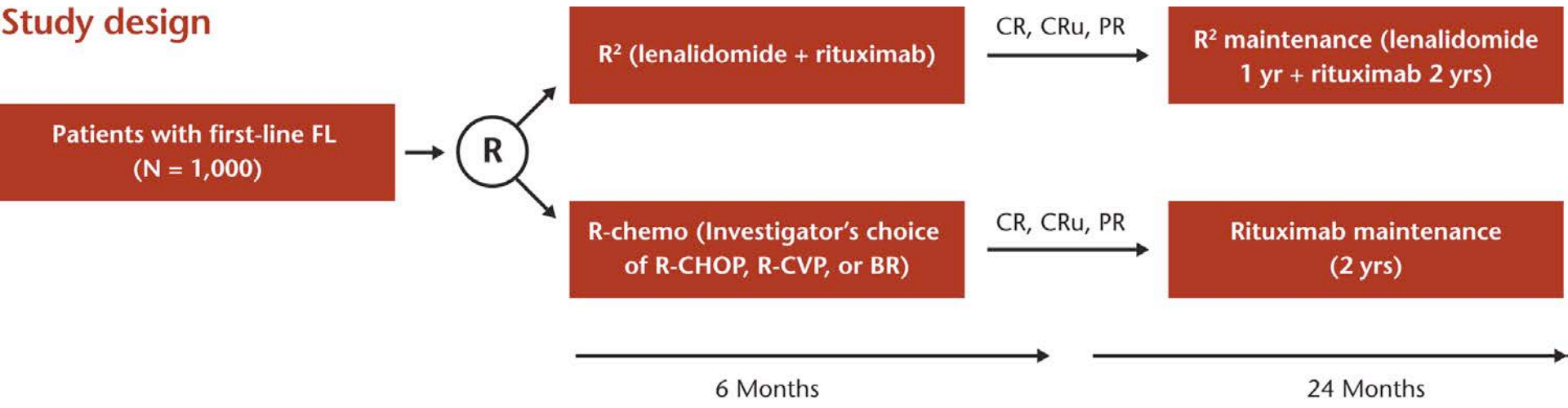


openi.nlm.nih.gov

Lenalidomide and lymphoma

- Diffuse large B cell
- Follicular lymphoma
  - RELEVANCE Trial
- Mantle cell lymphoma
- Chronic lymphocytic leukemia (CLL)

RELEVANCE Trial



BR = bendamustine, rituximab; CR = complete response; CRu = complete response, unconfirmed; FL = follicular lymphoma; PR = partial response; R = randomize; R² = lenalidomide, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Coming to the JCC early in 2014

www.newevidence.com

Summary

- Traditional chemotherapy is still the primary modality of treatment with rituximab
- We are hoping to finally move beyond rituximab
- Many new promising therapies coming down the pipeline
- We hope that these make to clinical trials and are successful
- Combinations of agents will probably be most useful