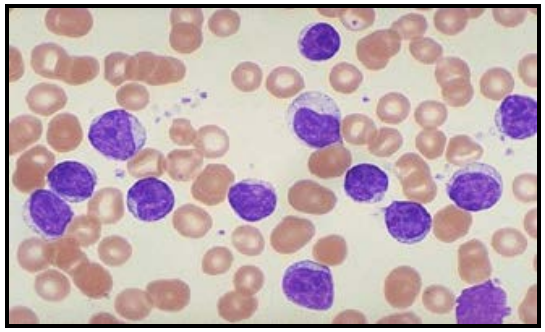
CLL AND IMMUNE DYSFUNCTION

CANADIAN RESEARCH PERSPECTIVE

Dr Spencer Gibson
Department of Oncology
University of Alberta



My Talk Outline

1. Why is the immune system not working well?
2. Can we improve the immune system?
3. What Canadian CLL research is being done?

Question about immune dysfunction.

How many people had infections that required antibiotics and/or hospitalization?

Infections and CLL patients

- **CLL patients are more likely to get infections.**
- **About 80% of CLL patients will have infection complication during their disease.**

- **Question: Do you have to have active disease to get infections?**

Leukemia (2021) 35:239–244
https://doi.org/10.1038/s41375-020-0799-8

LETTER

Chronic lymphocytic leukemia

Risk of serious infection among individuals with and without low count monoclonal B-cell lymphocytosis (MBL)

Tait D. Shanafelt[1] · Neil E. Kay[2] · Sameer A. Parikh[2] · Sara J. Achenbach[2] · Connie E. Lesnick[2] · Curtis A. Hanson[2] · Geffen Kleinstern[2] · Janet E. Olson[2] · Aaron D. Norman[2] · Kari G. Rabe[2] · Susan M. Schwager[2] · Timothy G. Call[2] · Susan L. Slager[2]

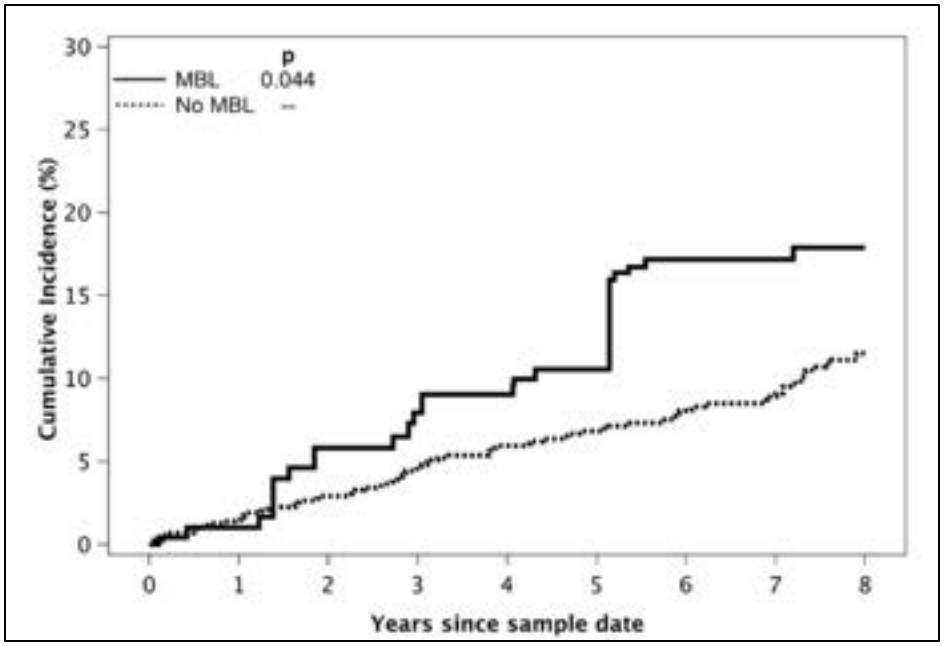
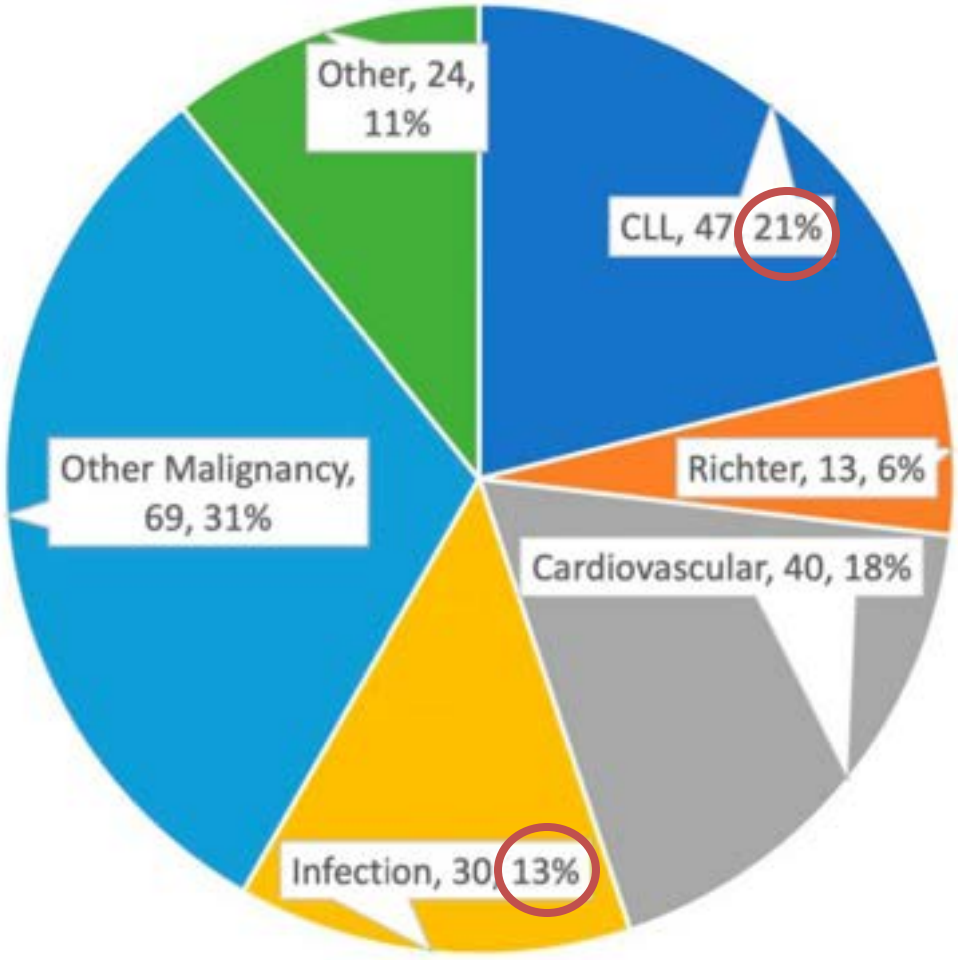


Fig. 1 Clinical outcomes of individuals with monoclonal B-cell lymphocytosis (MBL) compared to those without MBL. a Cumulative incidence of hospitalization for infection among individuals with ($n = 106$) and without MBL ($n = 865$) adjusted for age and sex. **b**

8 yr cumulative serious infections:
MBL 23%
Control 11%

- Pneumonia
- Blood stream
- UTI
- Cellulitis

Causes of death in CLL in Manitoba



1/3 second cancers
1/3 CLL/infections
1/3 other

Yang, L et al. Current Oncol, 30:6411, 2023

Why CLL patients have lousy immune systems?

1. CLL cells crowd out immune systems in the bone marrow and lymph nodes preventing immune cells functions.
2. CLL cells interact with immune cells causing them to be inactive or exhausted.
3. Immune cells provide support to CLL cells allowing them to survive and grow.

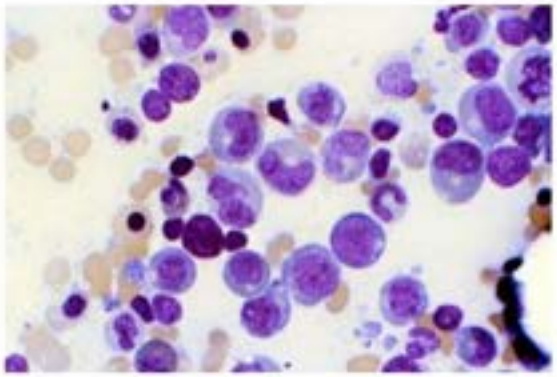
Immunology 101

- I am not a trained immunologist but still research it.
- Two main ways the immune system fights infections.
  - B cells: Produces antibodies against bacteria and viruses.
  - T cells: Kills cells invaded by viruses or cancer cells.

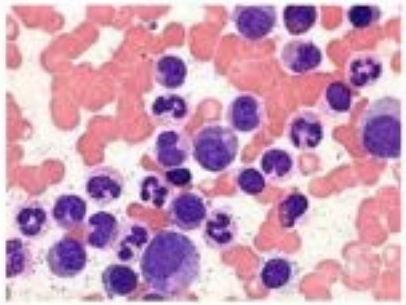
- In CLL
  - B cells that do not produce antibodies because CLL cells crowded them out.
  - T cells do not kill infected cells because CLL cells make them exhausted.

CLL crowding!

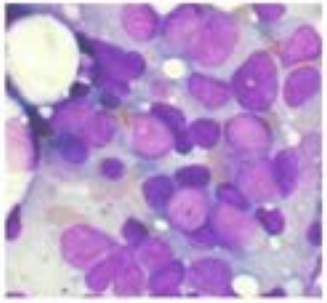
Normal bone marrow and CML, AML, CLL



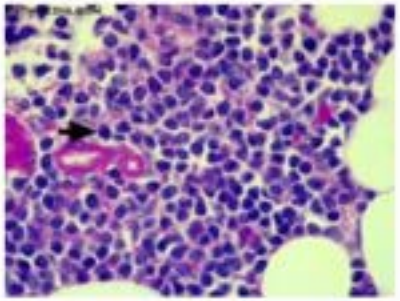
CML



AML

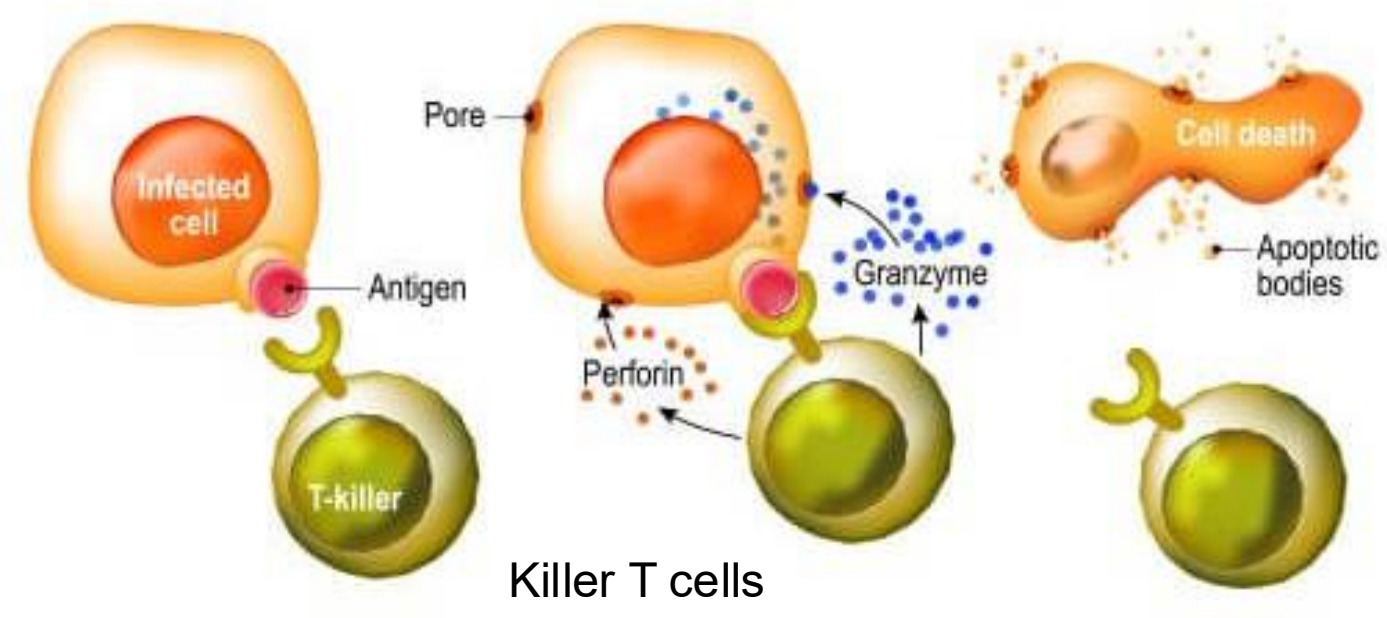


CLL



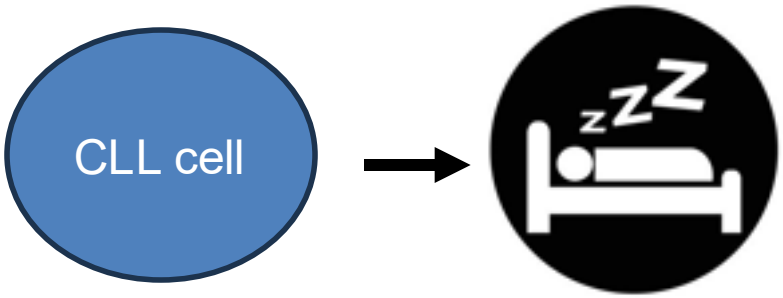
CROWDED!

Normal



Killer T cells

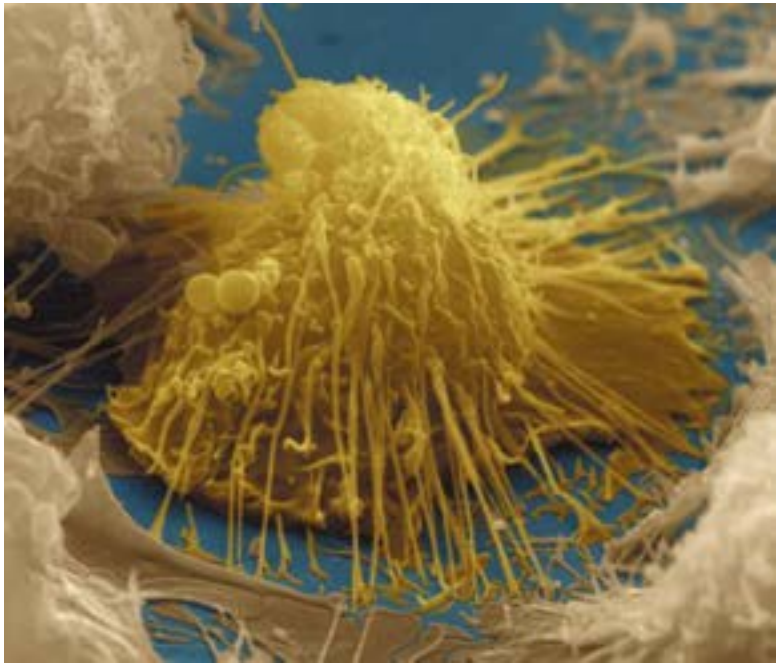
CLL

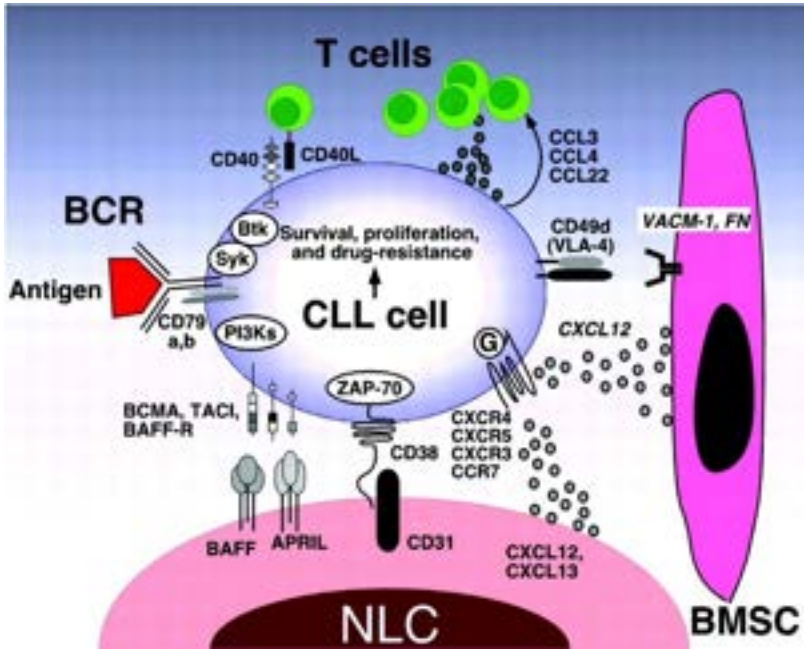


Exhausted T cells

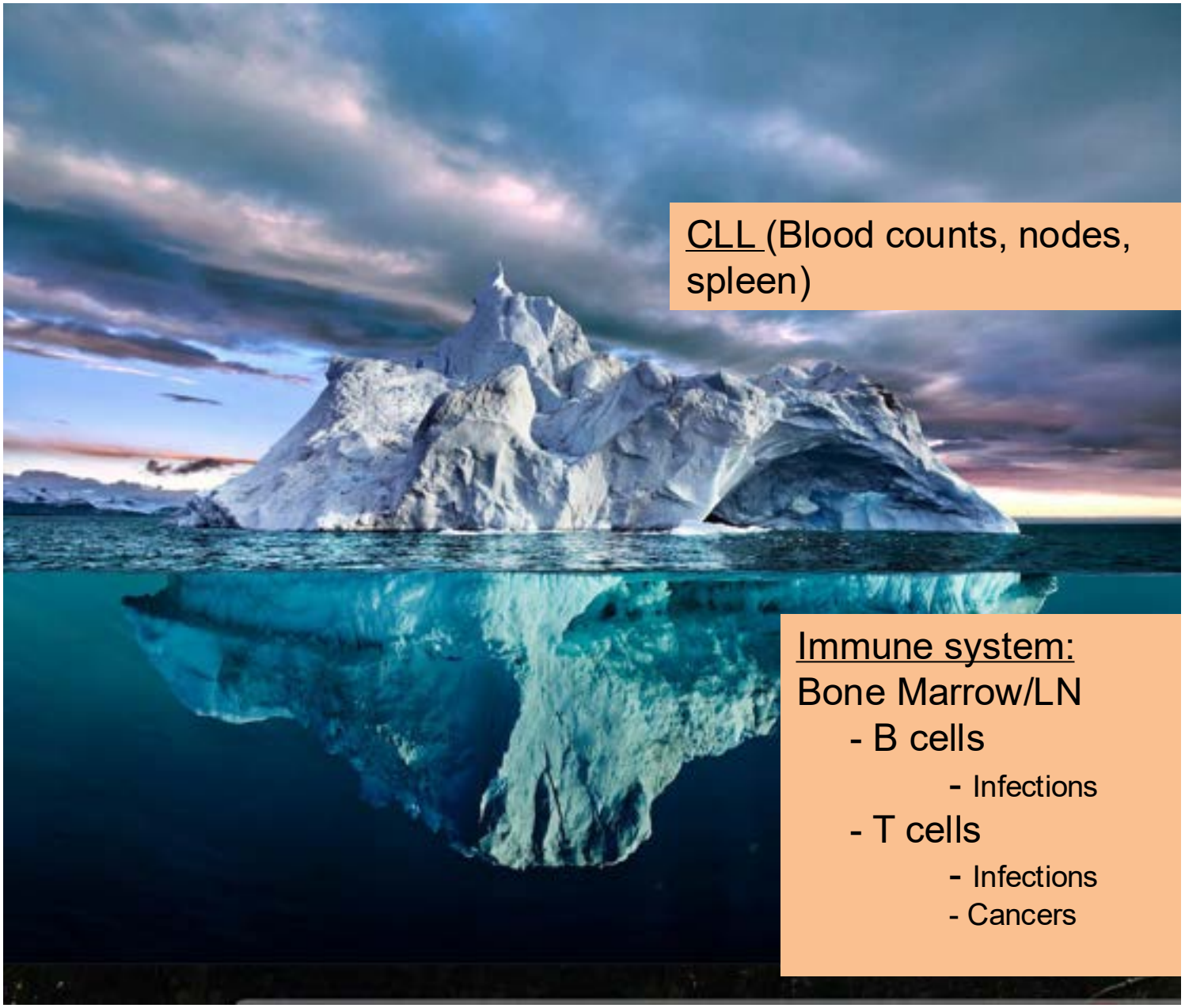
[Cytotoxic T Cell - The Definitive Guide | Biology Dictionary](biologydictionary.net)

Immune cells drive CLL cell survival and proliferation

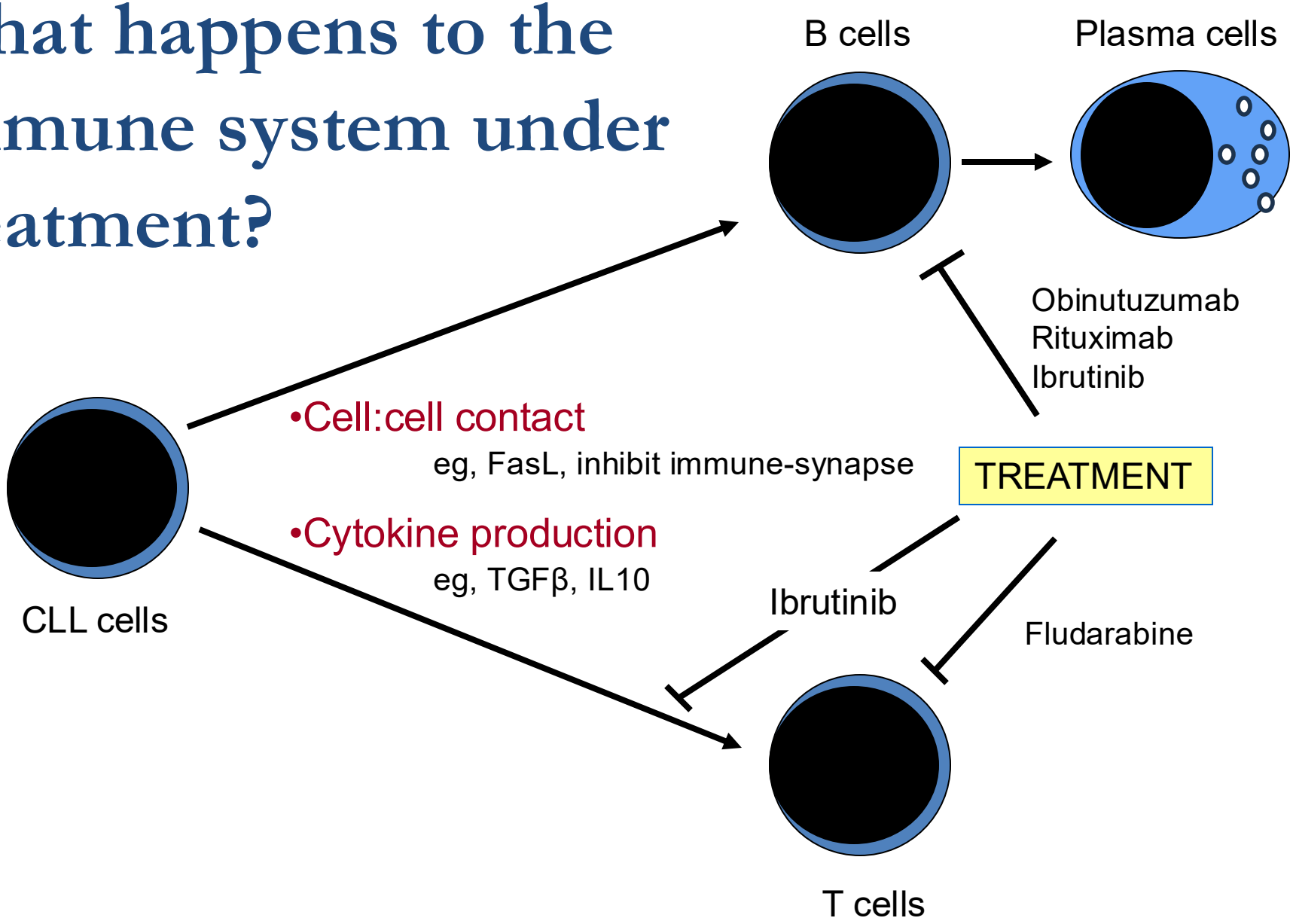




Gitlin et al. Nature, 517:139, 2015
Burger et al. Blood,114:3367, 2009

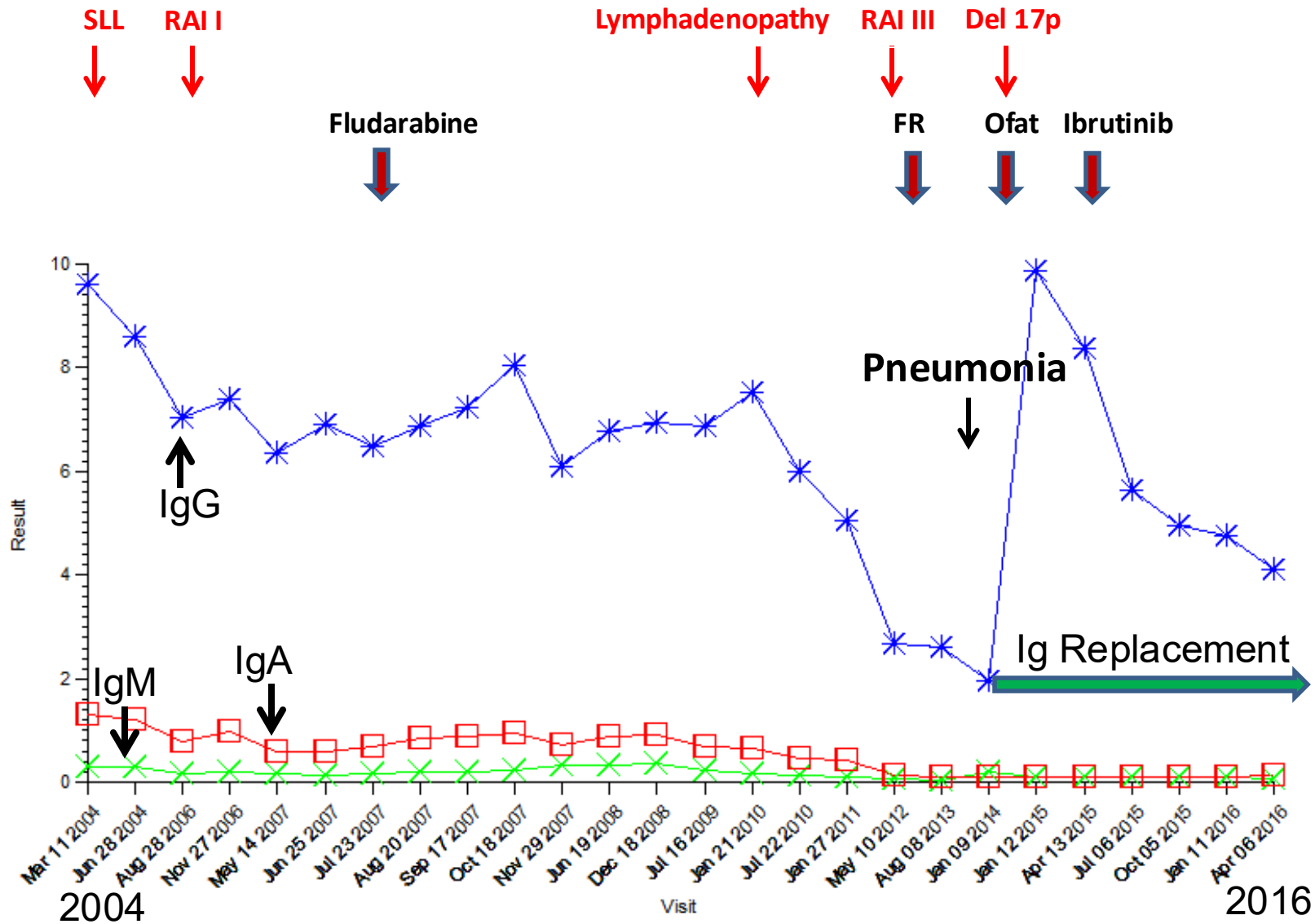

CLL (Blood counts, nodes, spleen)
Immune system:
Bone Marrow/LN
- B cells
- Infections
- T cells
- Infections
- Cancers

What happens to the immune system under treatment?



Forconi et al, Blood,126, 573, 2016

Antibody changes during disease progression



REGULAR ARTICLE

blood advances

IgA levels at diagnosis predict for infections, time to treatment, and survival in chronic lymphocytic leukemia

[redacted] S. Dhaliwal,[4] Salaheddin M. Mahmud,[5-7] Spencer B. Gibson,[1,8,9] Versha Banerji,[1,4] Aaron J. Marshall,[9] and James B. Johnston[1,4]

[redacted] Department of Epidemiology, CancerCare Manitoba, Winnipeg, MB, Canada; and [4]Section of Haematology/Oncology, Department of Internal Medicine, [5]Department of Community Health Sciences, [6]Vaccine and Drug Evaluation Centre, [7]College of Pharmacy, [8]Department of Biochemistry and Medical Genetics, and [9]Department of Immunology, University of Manitoba, Winnipeg, MB, Canada

*

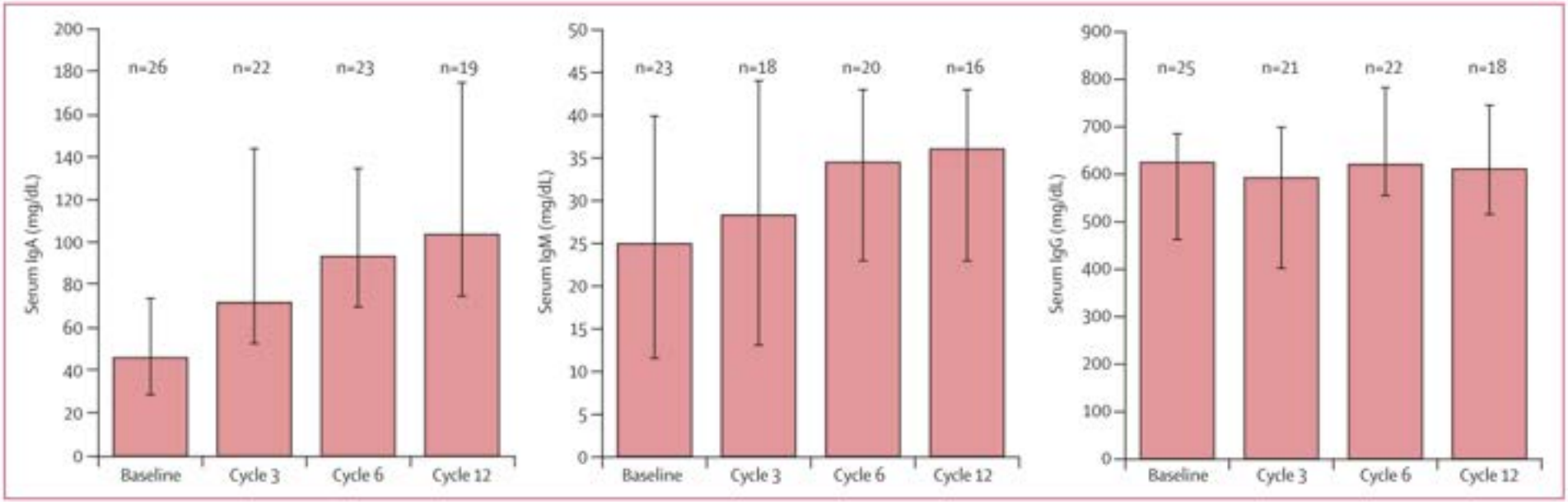
Key Points

- Abnormal levels of IgA at diagnosis predict time to treatment, survival, and need for immunoglobulin replacement in CLL.
- Abnormal levels of IgG at diagnosis predict the need for immunoglobulin replacement in CLL.

To better understand the relationship between baseline immunoglobulin measurements and subsequent clinical outcomes in chronic lymphocytic leukemia (CLL), we performed a retrospective analysis on 660 patients with CLL (72%), monoclonal B-cell lymphocytosis (MBL) (13%), and small lymphocytic lymphoma (SLL) (14%), diagnosed between 2005 and 2014 at CancerCare Manitoba. Of 511 patients who had their first immunoglobulin level determined within 3 months of diagnosis, abnormal (either increased or decreased) immunoglobulin M (IgM), IgG, and IgA values were observed in 58% of patients with CLL, 27% of patients with MBL, and 20% of patients with SLL. Immunoglobulin deviances were similar for MBL and CLL Rai stage 0 and for SLL and Rai stages I and II; for CLL, IgG and IgA abnormalities occurred with increasing frequency with advancing Rai stage. In contrast, the frequency of IgM abnormalities was similar in all patient groups. IgA abnormalities significantly correlated with high β2-microglobulin (B2M) expression,

Ishdorj et al. Blood Advances, 3:2188, 2019.

Research Questions: Does CLL remission from targeted therapies restore the immune system?



IgA increases after ibrutinib therapy

O'Brien, et al. Lancet Oncology, 115:48, 2014

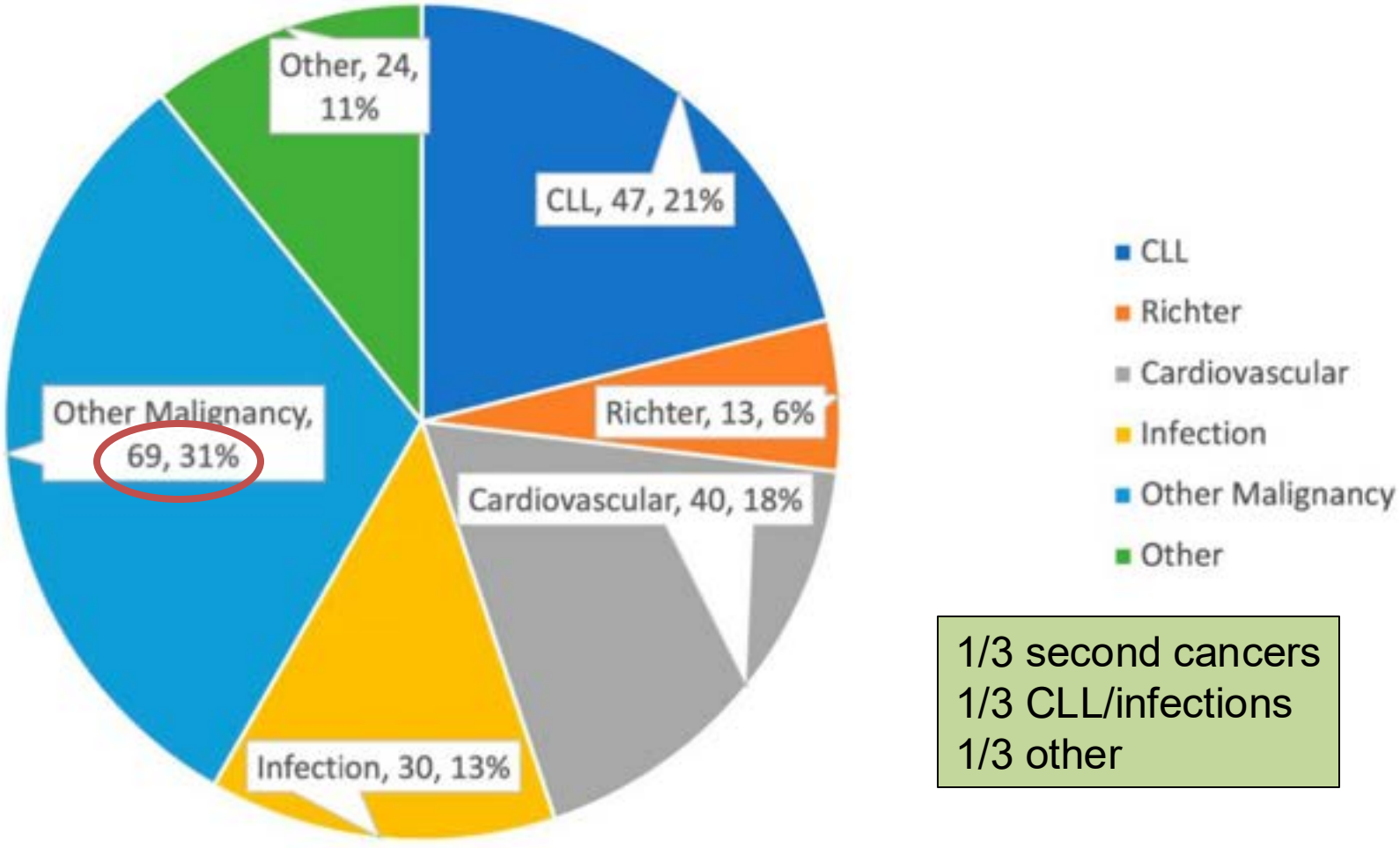
Summary I

- CLL patients get infections.
- Due to crowding out immune cells and inactivating immune cells.
- Antibodies decreased over time.
- Treatments impact immune system.

Question about immune dysfunction:

- How many people know of someone who got a second cancer after CLL diagnosis?

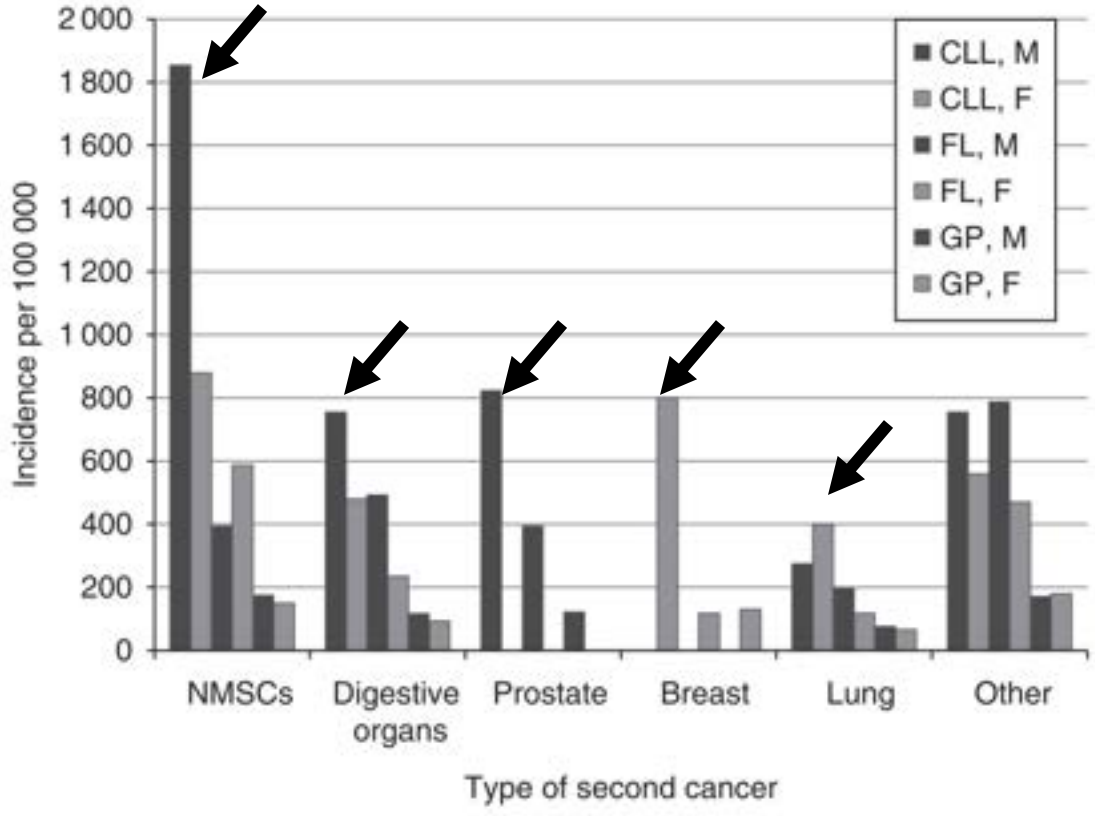
Causes of death in CLL in Manitoba



1/3 second cancers
1/3 CLL/infections
1/3 other

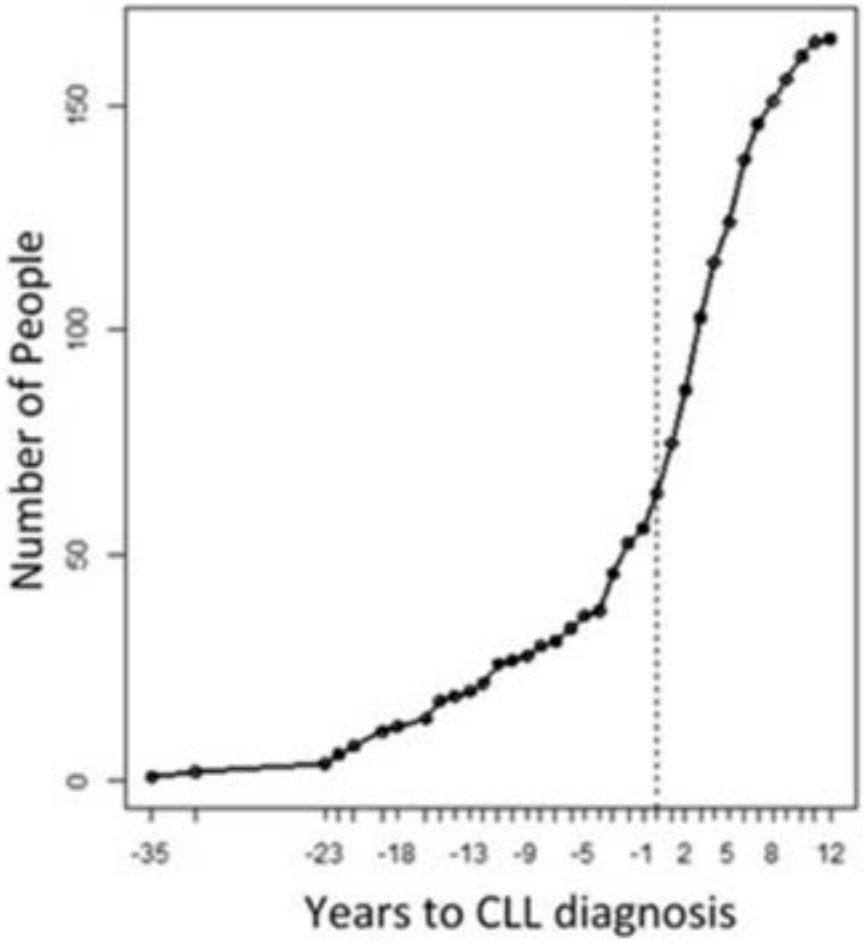
Yang, L et al. Current Oncol, 30:6411, 2023

Compared CLL with follicular lymphoma and age-/sex-matched general population to eliminate surveillance bias



Beiggi, s et al. Br J Cancer, 109:1287, 2013

Incidence of skin cancers started increasing prior to diagnosis of CLL



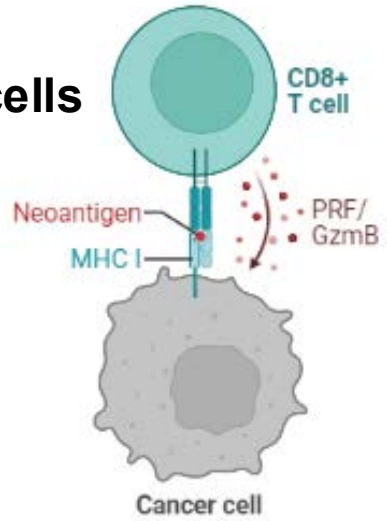
WHY?

Beiggi, s et al. Br J Cancer, 109:1287, 2013

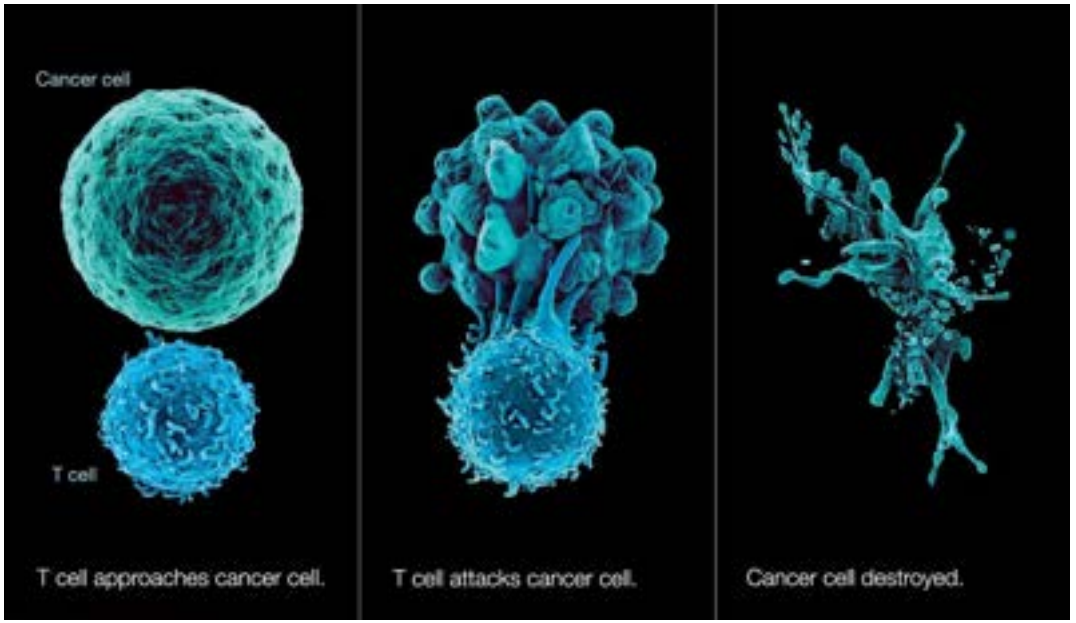
Immune system and cancer!

- The immune system monitors for cancer cells and kills them all the time.

Killer T cells

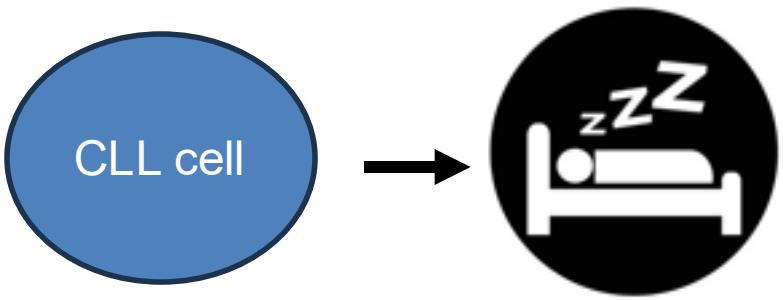


Cell Death

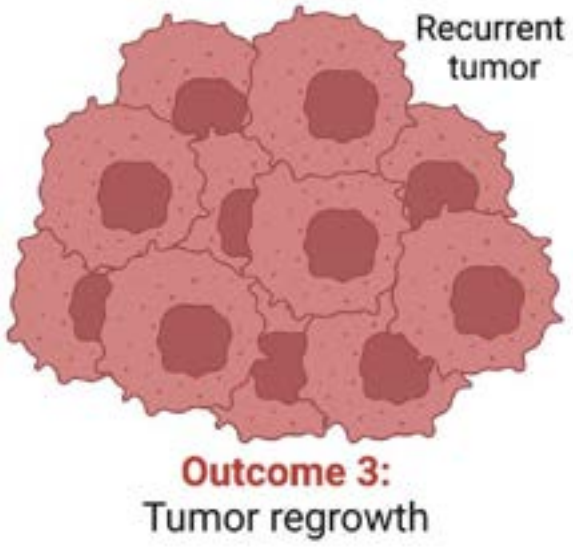


[Aging Breakthroughs: Senescent Cell Removal – QYRAL](qyral.com)

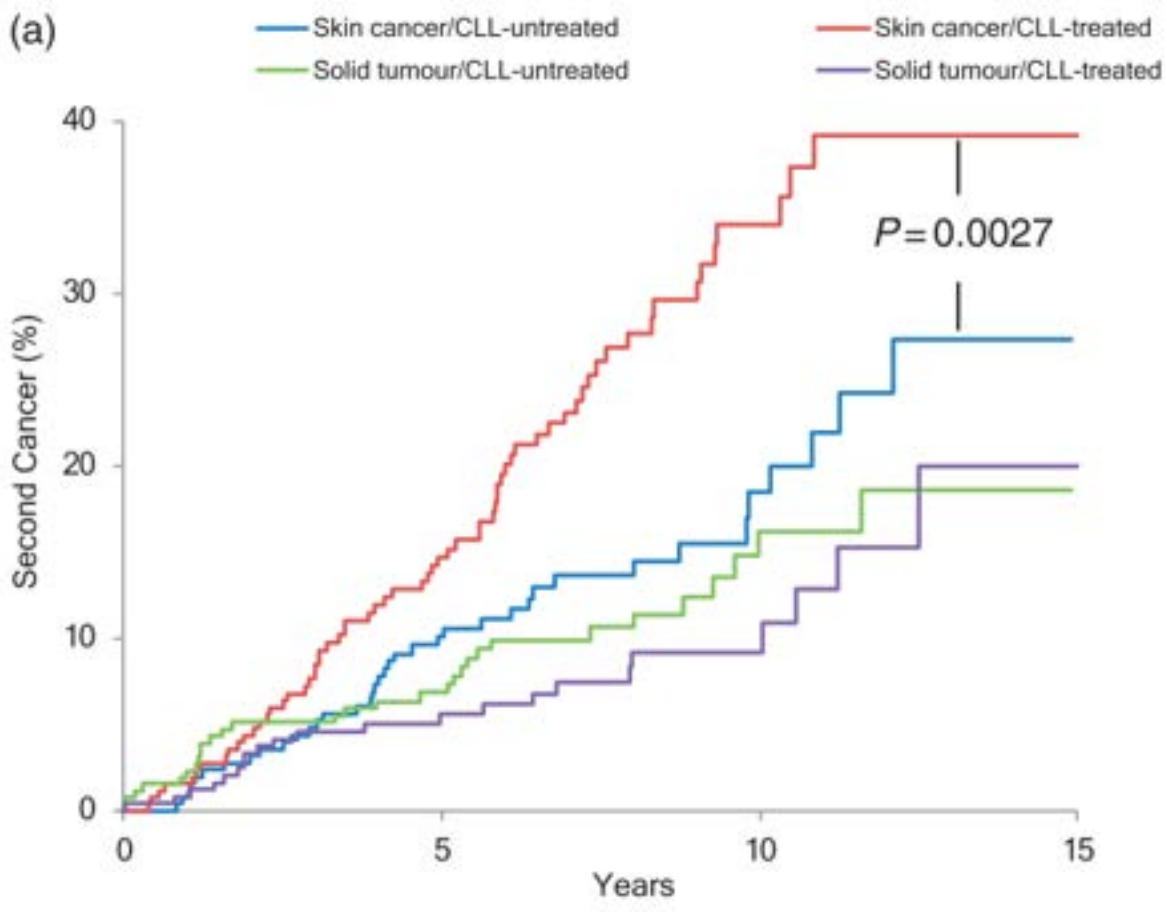
CLL immune system and cancer



Second Cancer



Incidence of skin cancers but not solid tumors increased by chemotherapy



Beiggi, s et al. Br J Cancer, 109:1287, 2013

Second cancer incidence in CLL patients receiving BTK inhibitors

David A. Bond[1] · Ying Huang[1] · James L. Fisher[2] · Amy S. Ruppert[1] · Dwight H. Owen[3] · Erin M. Bertino[3] · Kerry A. Rogers[1] · Seema A. Bhat[1] · Michael R. Grever[1] · Samantha M. Jaglowski[1] · Kami J. Maddocks[1] · John C. Byrd[1] · Jennifer A. Woyach[1]

Received: 31 December 2019 / Revised: 10 July 2020 / Accepted: 14 July 2020

Abstract

Chronic lymphocytic leukemia (CLL) is associated with perturbed immune function and increased risk for second primary malignancies (SPM). Ibrutinib and acalabrutinib (BTKi) are effective therapies for CLL resulting in partial restoration of immune function. The incidence of and risk factors for SPM in CLL patients receiving BTKi are not yet characterized. We retrospectively determined the incidence of SPM in CLL patients treated with ibrutinib or acalabrutinib at our institution between 2009 and 2017, assessed for association between baseline characteristics and SPM incidence, and compared the observed to expected cancer incidence among age, sex, and year matched controls without CLL. After a median of 44 months follow-up, 64/691 patients (9%) were diagnosed with SPM (excluding non-melanoma skin cancer [NMSC]). The 3-year cumulative incidence rate was 16% for NMSC and 7% for other SPM. On multivariable analysis, smoking was associated with increased SPM risk (HR 2.8 [95% CI: 1.6–4.8]) and higher baseline CD8 count was associated with lower SPM risk (HR 0.9 for 2-fold increase [95% CI: 0.8–0.9]). The observed over expected rate of SPM was 2.2 [95% CI: 1.7–2.9]. CLL patients treated with BTKi remain at increased risk for SPM, and secondary cancer detection is an important consideration in this population.

Bond et al. Leukemia, 34:3197, 2020

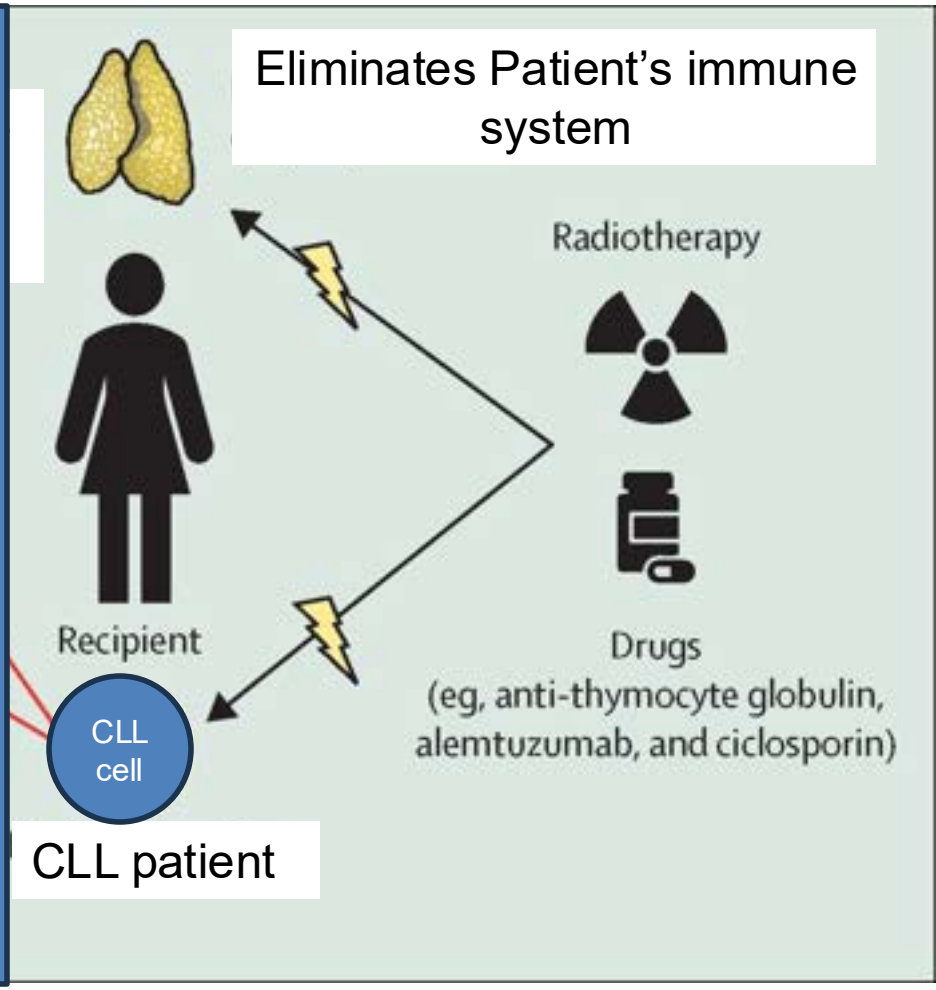
Summary II

- CLL patients get second cancers.
- Mainly due to T cell exhaustion.
- Targeted treatments may not restore the immune system to prevent second cancers.
- Self-care and Secondary Cancers, Ms. Nanette Cox-Kennett, Nurse Practitioner, Alberta Health Services

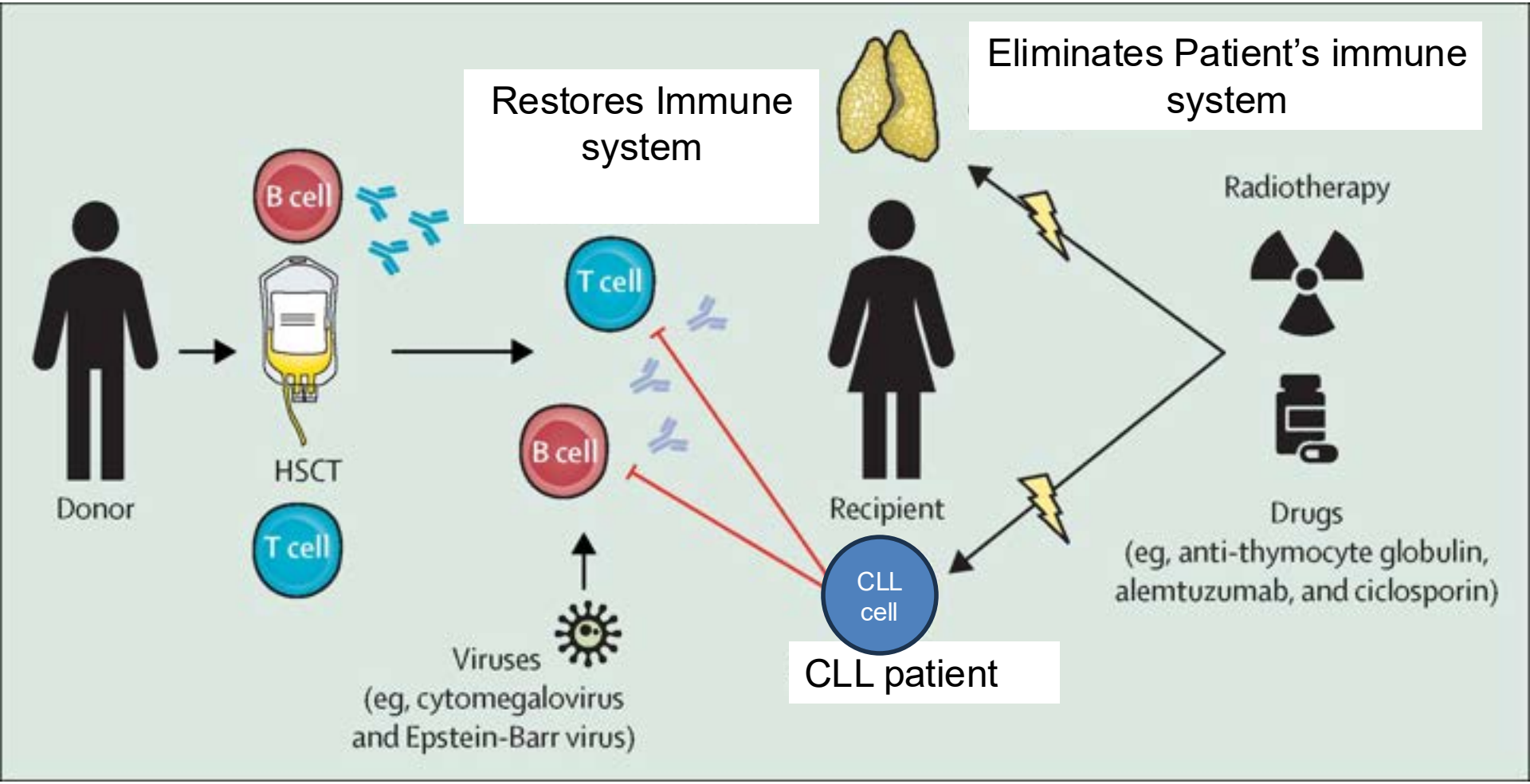
Can we improve the immune system?

1. Vaccinations against common infections (Self-care. Ms. Nanette Cox-Kennett).
2. Bone marrow transplantation
3. Immuno-therapy
    - CAR-T cells

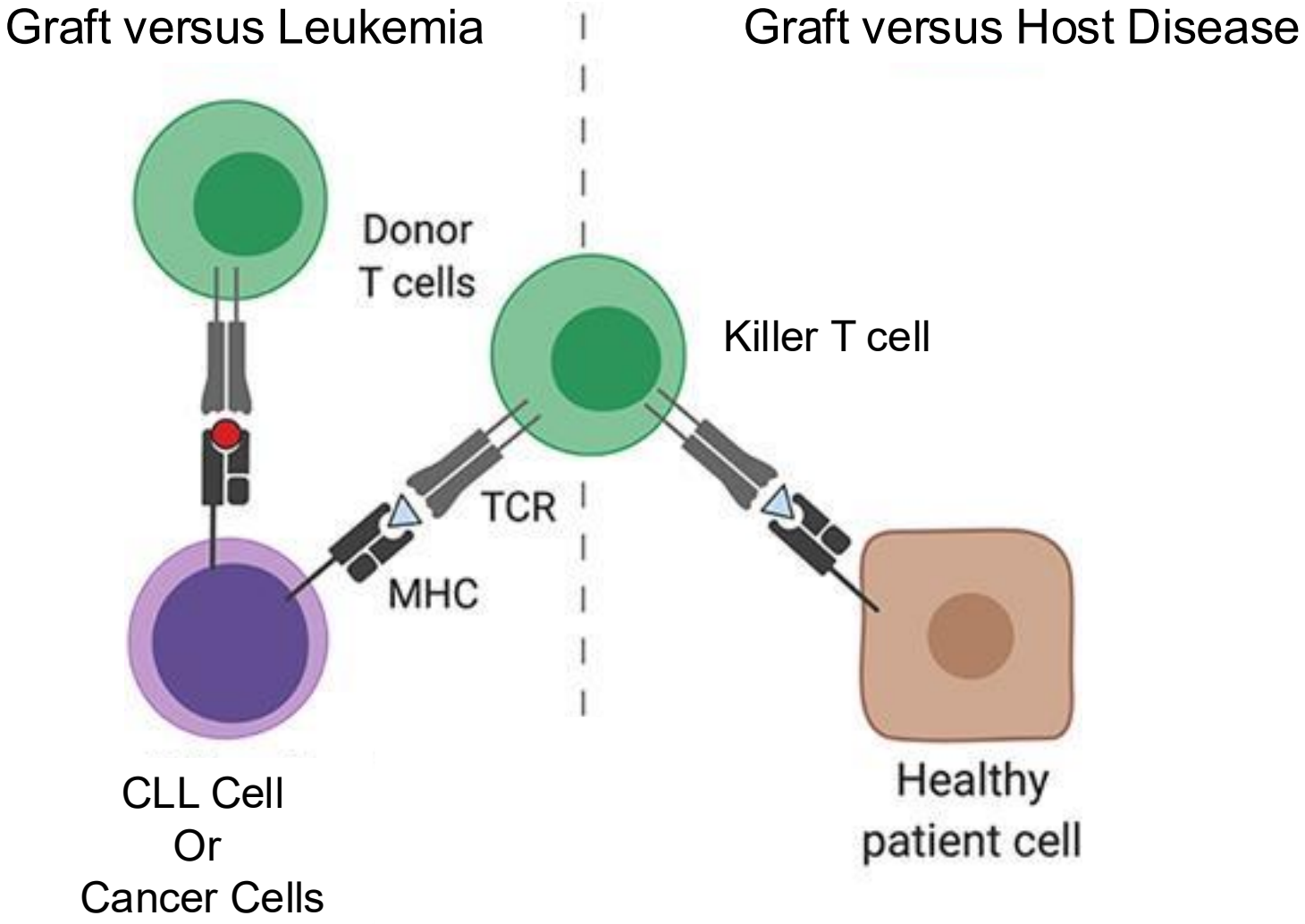
Bone marrow transplant: Immune system is depleted!



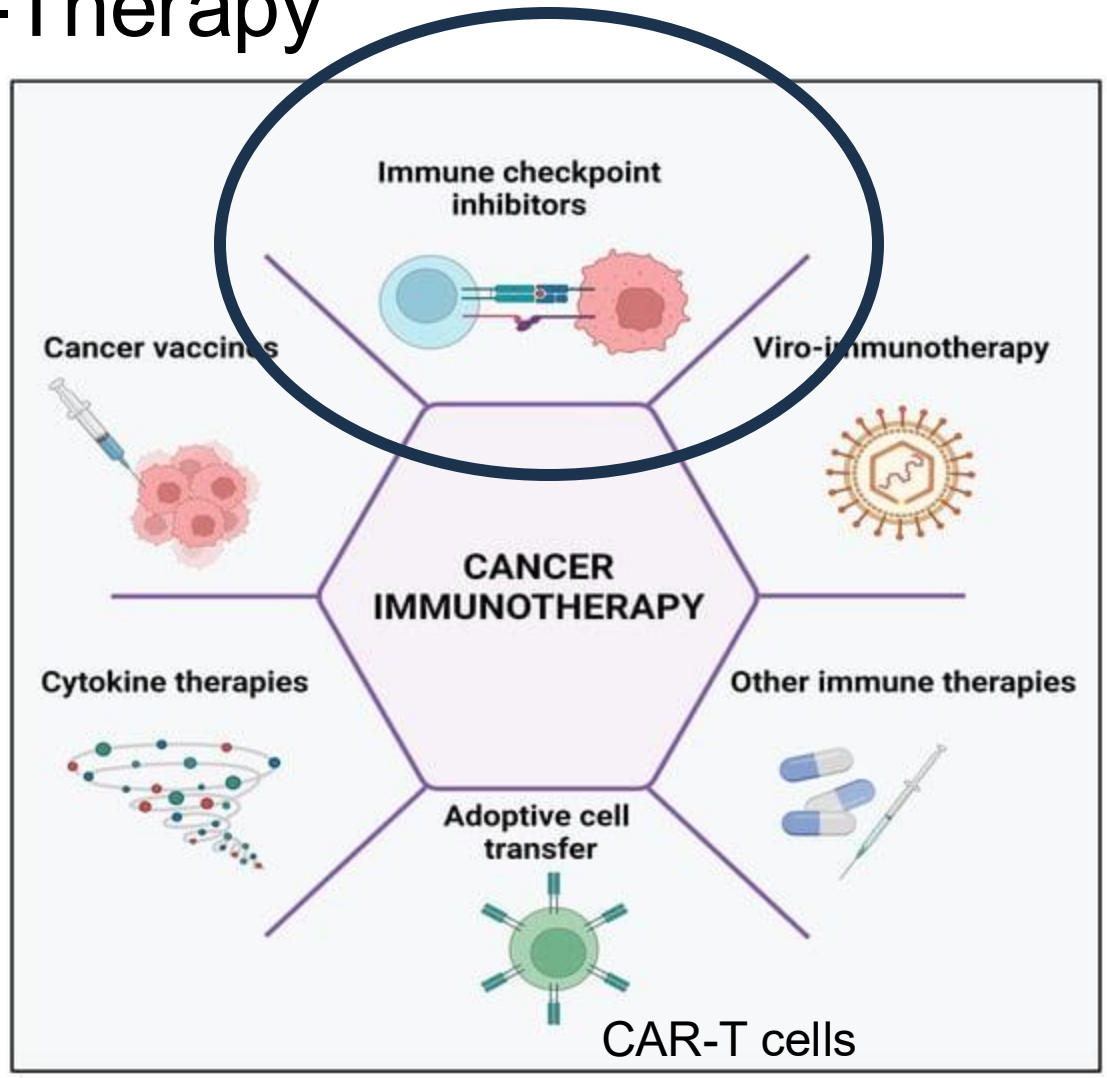
Bone Marrow Transplant: Immune system is replaced!



“Jekyll and Hyde” Problem



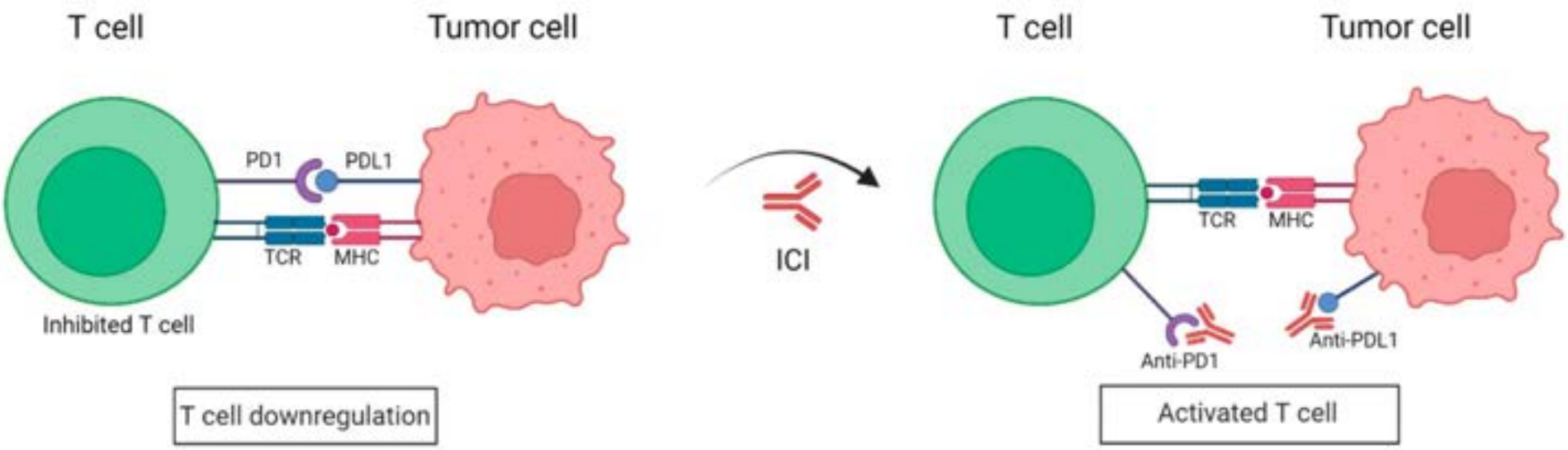
Immuno-Therapy

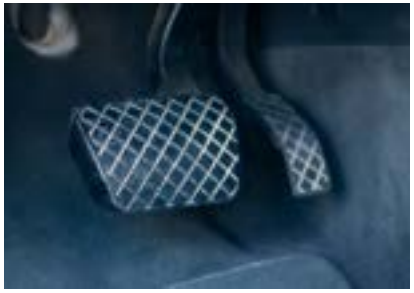


[Cancers | Free Full-Text | Recent Advances in Molecular Mechanisms of Cancer Immunotherapy]

Untreated

Immuno-therapy



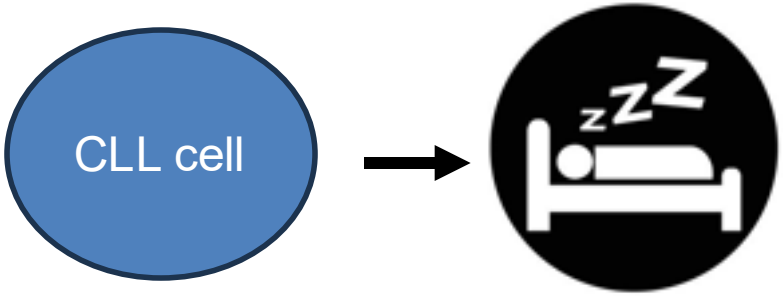


Like a brake in a car

Does Immuno-therapy work in CLL?

[Self-reactive, innate-like T cells enhance cytotoxicity and immunosurveillance: Trends in Cancer](cell.com)

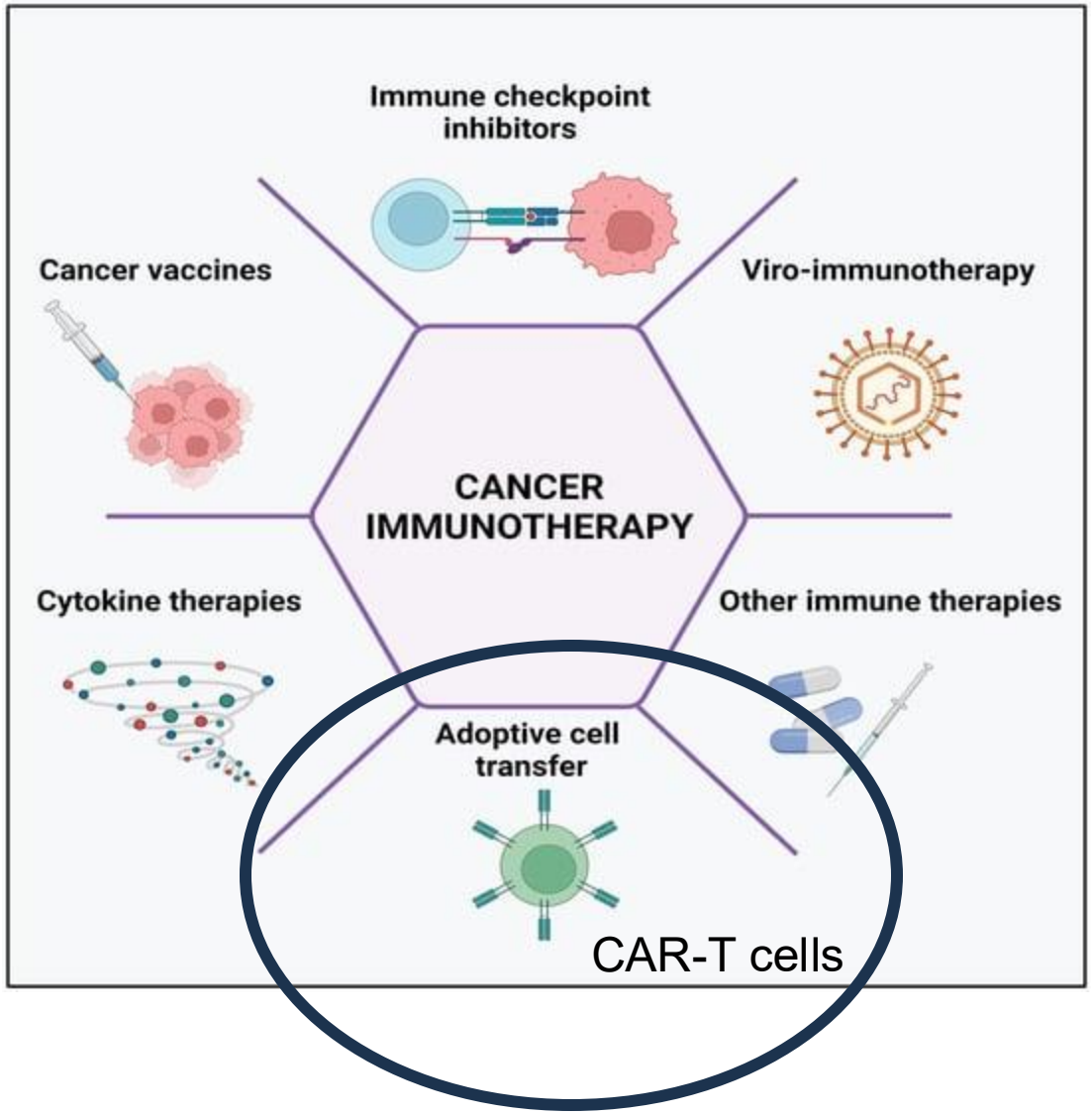
CLL immune system



Exhausted T cells

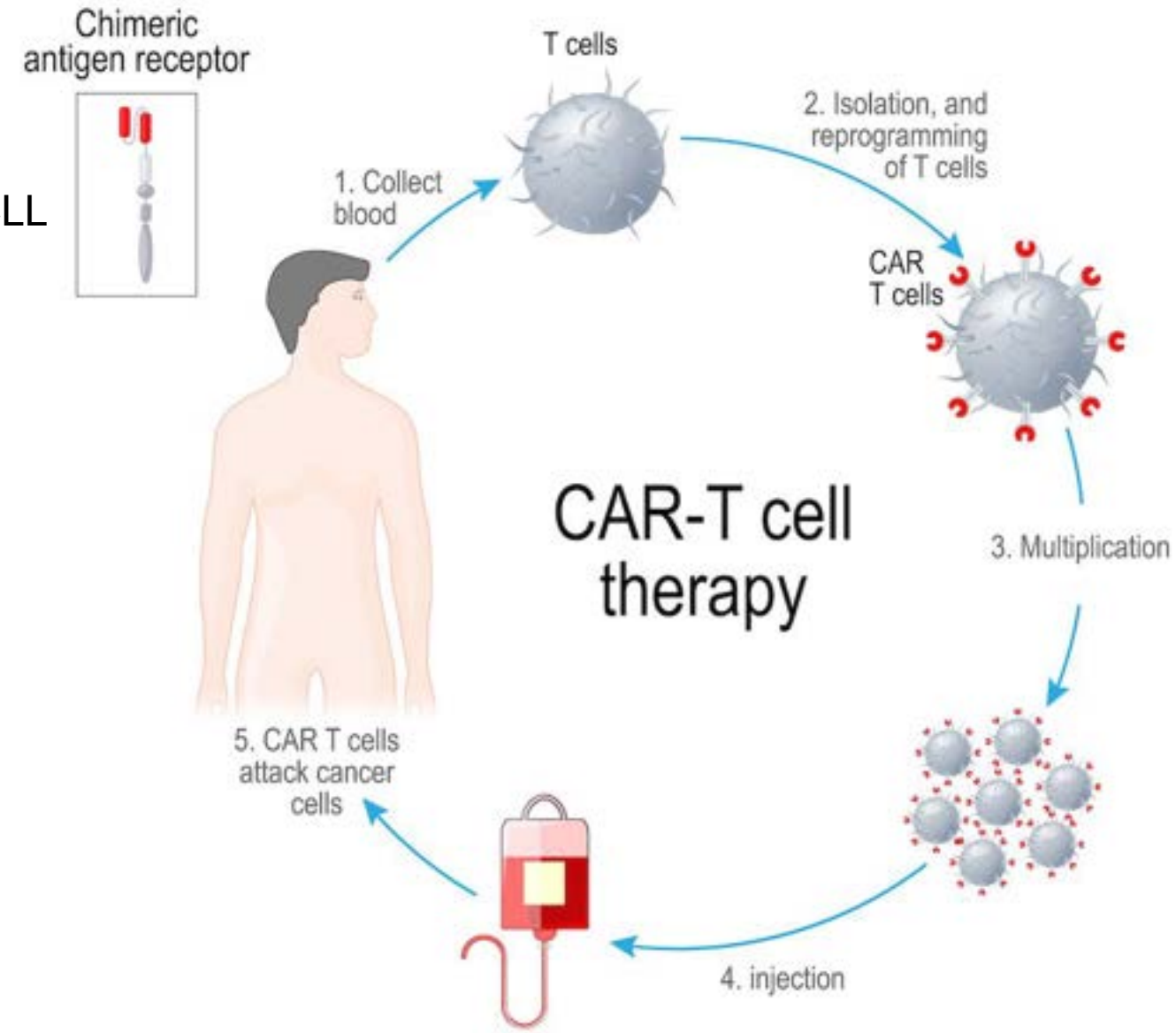
Immune Checkpoint Inhibitors <u>failed</u> in clinical trials to treat CLL

Immuno-Therapy



Waking up T cells

Anti-CD19
target for CLL



CAR-T cells in CLL

Promise:

- CAR-T cell therapy give overall complete response rate between 20-70% depending on the clinical trial.
- Given to patients that relapsed from previous treatments.
- Combination with BTKi seems effective.
- FDA approved anti-CD19 CAR-T cells for double refractory CLL patients.

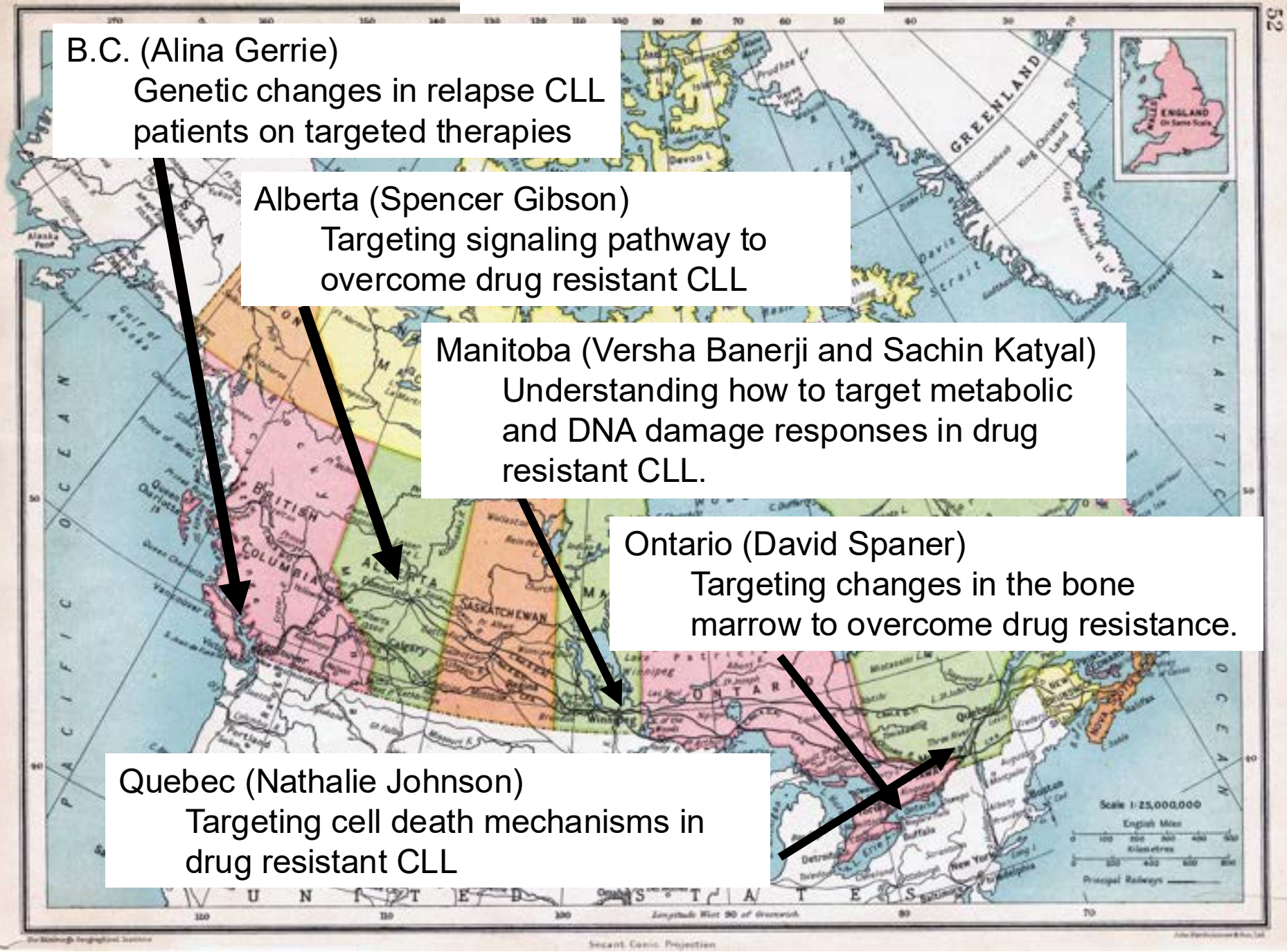
Challenges:

- Significant toxicities exist including cytokine storm and autoimmunity.
- Long term survival and toxicity are unknown.
- Cost remains a barrier.

Summary III

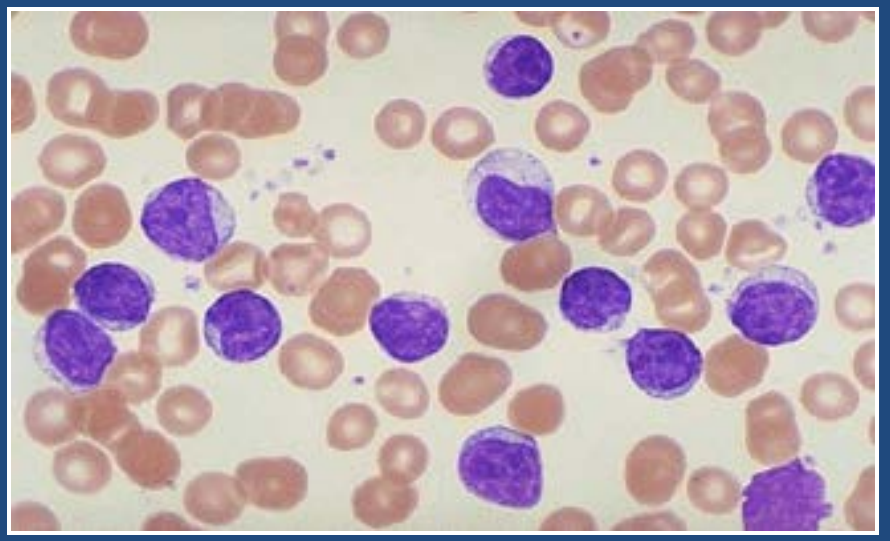
- Bone marrow transplantation can cure CLL through Graft versus Leukemia effect.
- Graft versus Host disease still an issue.
- Immuno-checkpoint therapy does not work.
- CAR-T cells show promise against CLL.
  - FDA approved for double refractory disease.

Canadian CLL Research:



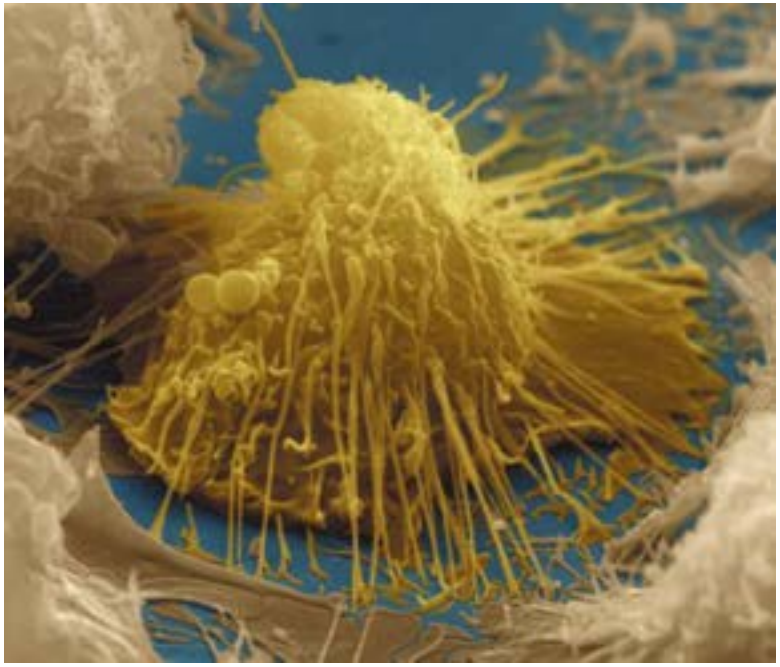
Questions being addressed!

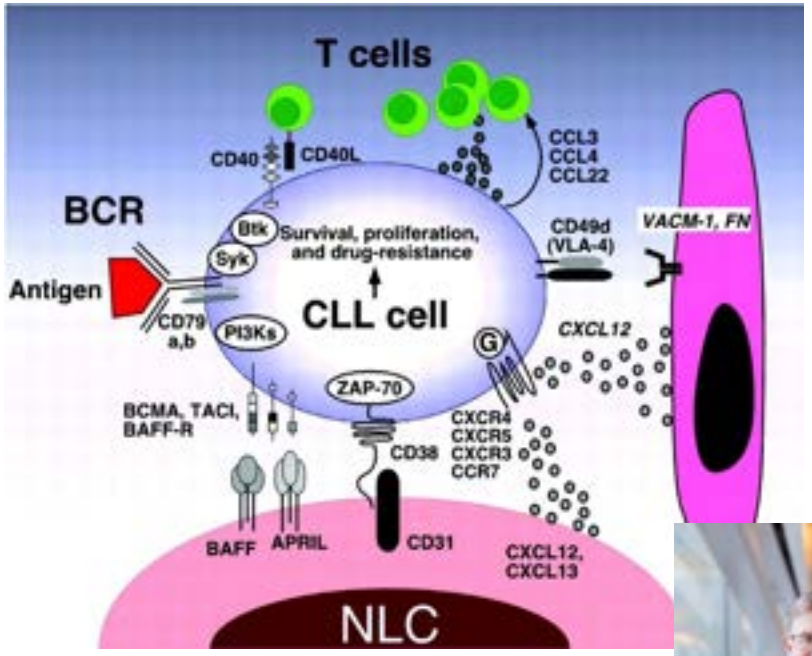
1. Understand the CLL in the bone marrow and lymph nodes?
2. Developing better treatment strategies to prevent or treat drug resistant CLL.
3. How create access to Canadian patients for new drugs to treat drug resistant CLL. (Caroline Owen, Versha Banerji)



QUESTIONS

Immune cells drive CLL cell survival and proliferation





Gitlin et al. Nature, 517:139, 2015
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